DATA EVALUATION RECORD

TEBUCONAZOLE

Study Type (§83-6a): Developmental Neurotoxicity Study in the Rat

Work Assignment No. 2-01-72 A (MRID 45074301)

Prepared for

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DATA EVALUATION RECORD

STUDY TYPE: Developmental Neurotoxicity Study-rats

OPPTS Number: 870.6300 OPP Guideline Number: §83-6a

DP BARCODE: D264727 SUBMISSION CODE: S577006
P.C. CODE: 128997 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): Tebuconzaole (96-96.9% a.i.)

SYNONYMS: H-1,2,4-triazole-1-ethanol
a-[2-(4-chlorophenyl)-ethyl]-*a*-(1,1-dimethylethyl)-±(CAS)

CITATION: Parker, R.M., (2000) Developmental Neurotoxicity Study of Technical Grade Tebuconazole Administered Orally via Diet to Crl:CD®BR VAF/Plus® Presumed Pregnant Rats. Primedica Argus Research Laboratories, Inc., Horsham, PA. Lab. Study No. 1702-004; Sponsor's Study Number 98-C612-QU, March 1, 2000. MRID 45074301. Unpublished.

SPONSOR: Bayer Corporation, Kansas City, MO

EXECUTIVE SUMMARY: In a developmental neurotoxicity study (MRID 45074301), tebuconazole (96-96.9% a.i.; Lot/Batch #603-0013) in corn oil was administered via the diet to pregnant Crl:CD®BR VAF/Plus® (Sprague Dawley) rats (25/dose) from gestation day (GD) 6 to lactation day (LD) 11 at doses of 0, 100, 300 or 1000 ppm (equivalent to [GD/LD] 0/0, 8.8/16.3, 22.0/41.3, and 65.0/125.4 mg/kg/day). No analytical data were provided. P dams were allowed to deliver naturally. On day 5 postpartum, litters were standardized to a maximum of 10 pups/litter. Pups were assigned to one of 5 Subsets (20 pups/sex/dose in each subset). Physical development landmarks were evaluated for all subsets (including surface righting, eye opening, pinna unfolding, acoustic startle response, and pupil constriction); sexual maturation was evaluated in subsets 2-4. Subset 1 pups were sacrificed on postnatal day 12; brains were weighed for all Subset 1 pups, and histopathological evaluations were performed on 6/sex in control and high dose groups (morphometric analysis was performed on 6/sex in control,

mid-dose, and high dose groups). Subset 2 pups were evaluated for learning and memory on day 23-25 (passive avoidance) and on day 59-63 (Water M-maze). Subset 3 pups were evaluated for motor activity (days 14, 18, 22, and 62) and for auditory startle habituation (days 23 and 63). Subset 4 pups received detailed weekly clinical evaluations. In addition, 6 animals/sex/group in Subset 4 were selected for neuropathological evaluations; brains were weighed and the high dose and control animals were evaluated histopathologically on day 83 (morphometric analysis was performed on 6/sex in control, mid dose, and high dose groups). Subset 5 pups were sacrificed and necropsied on day 22.

At 1000 ppm, two P females died as a result of prolonged gestation. Body weights were slightly decreased ($p \leq 0.01$) in the P females during gestation (↓4-8%) and early lactation (↓6-12%). Body weight gains were decreased ($p \leq 0.01$ or 0.05) during GDs 6-9 (↓400%) and 6-21 (↓22%), and during LDs 1-12 (↓55-164%). When compared to concurrent controls, absolute (g/animal/day) food consumption was reduced ($p \leq 0.05$ or 0.01) in the dams throughout gestation (↓9-23%) except during the GD 0-6 interval, and during the LD intervals 4-7 (↓20%) and 7-12 (↓18%). Relative (g/kg/day) food consumption was reduced ($p \leq 0.05$ or 0.01) starting on GD 6 (6-20%) and during early lactation (up to day 12, (↓8-12%). There was also an increase in alopecia in high dose dams. The number of live fetuses/dam was decreased relative to concurrent controls (↓6%, $p \leq 0.01$); while the number of dead fetuses/dam was increased relative to concurrent controls (↑200%, $p \leq 0.01$).

No treatment-related findings were observed in dams at 300 or 100 ppm.

The LOAEL for maternal toxicity is 1000 ppm (equivalent to [GD/LD] 65.0/125.4 mg/kg/day) based on decreased body weights, body weight gains, and food consumption, prolonged gestation with mortality, and an increased number of dead fetuses. The NOAEL is 300 ppm (equivalent to [GD/LD] 22.0/41.3 mg/kg/day).

At 1000 ppm, the stillborn index was increased (↑200%, $p \leq 0.01$) and the number of pup deaths (calculated by reviewers) was increased during days 1-5 (↑229%). Body weights were decreased ($p \leq 0.01$) in the males from PND 5 to 86 (↓7-23%) and in the females from PND 5 to 72 (↓5-24%). Pinna unfolding was delayed (↑19%, $p \leq 0.01$) relative to concurrent controls. There were decreases in several morphometric measurements of the brain, including decreased ($p \leq 0.01$) thickness of the cerebellum in the males and females on day 12 (↓10-14%) and on day 83 (↓7-9%), and an increased thickness of the germinal layer of the cerebellar cortex in the Day 12 males (↑23%, $p \leq 0.01$). Absolute brain weights were decreased in the Day 12 and Day 83 animals (↓10-16%, $p \leq 0.01$ or 0.05). Relative (to body) brain weights were increased ($p \leq 0.01$ or 0.05) in the day 12 males and females (↑10-15%). There were also statistically significant changes in motor activity on days 14 (43% decrease in males [$p < 0.01$], 24% decrease in females [n.s.]) and 22 (39% increase in males [$p < .05$], 19% increase in females [n.s.]), and changes in auditory startle amplitude at both time points (decreased in both sexes on day 23 [14-33%], decreased in females [20%] and increased in males [71%] on day 63).

At 300 ppm, there were also decreases in body weight (3-7%) and body weight gain (4-16%, PND5-23 and 72-86 in males, PND5-51 in females). Pinna unfolding was delayed (↑16%). There were changes in auditory startle amplitude in both sexes: a dose-related decrease in females on day 23 (decreased 26%), and a dose-related increase in males on day 63 (increased 18%). In addition, there was a decrease in absolute brain weight in both sexes (3-4%) on day 12 (statistically significant for females only), and in brain measurements (anterior/posterior cerebrum).

At 100 ppm, there were decreases in body weight (3-7%) and body weight gain (5-13%) (PND 5-37 in males, PND 5-51 in females). There were decreases in motor activity (on days 14 and 18 in males [28-35%]) and changes in auditory startle amplitude (decreased 9% in day 14 females, increased 16% in day 63 males, n.s.). There was also a decrease in absolute brain weight in both sexes on day 12 (4%, statistically significant for both sexes), and in brain measurements (anterior/posterior cerebrum).

The LOAEL for offspring toxicity is 100 ppm based on decreases in body weights, decreases in absolute brain weights and measurements, and decreases in motor activity.

The NOAEL is not determined.

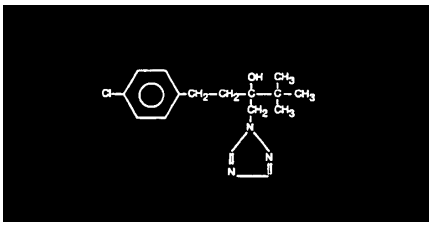
This study is classified as **acceptable/guideline (§83-6[a])** and satisfies the requirement for a developmental neurotoxicity study in rats, pending submission of additional information regarding analytical data and positive control studies, as described below.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Tebuconazole Technical
   Description: White powder
   Lot/Batch #: 603-0013
   Purity: 96-96.9% a.i.
   Stability: Stable in the diet for up to 14 days at room temperature and 36 days at -23ºC
   CAS #: 107534-96-3
   Structure:



2. Vehicle: Corn Oil/Diet

3. Test animals: Species: Rat
   Strain: Crl:CD®BR VAF/Plus® (Sprague Dawley)
   Age at start of dosing: Approximately 11 weeks
   Weight at start of dosing: 272-275 g
   Source: Charles River Laboratories, Inc. Raleigh, NC
   Housing: Animals were housed individually in stainless steel wire-bottomed cages except during the cohabitation and postpartum periods. During cohabitation, animals (1 male, 1 female) were housed in the male's cage; starting no later than gestation day 20, dams were housed in nesting boxes (with Bed-o'cobs bedding [The Andersons Industrial Products Group, Maumee, OH]). After weaning, the F1 generation pups were individually housed in stainless steel wire-bottomed cages.
   Diet: Certified Rodent Diet #5002 during acclimation, cohabitation, prior to gestation day 6, and after lactation day 11; dietary admixtures using Purina Mills Rodent Lab Chow #5001-4 , "etts," from gestation day 6 through lactation day 11 (PMI Nutrition International, St. Louis, MO), ad libitum.
   Water: Reverse-osmosis filtered tap water, ad libitum
   Environmental conditions:
      Temperature: 65.9-73.1°F
      Humidity: 42.4-74.2%
      Air changes: At least 10/hour of HEPA-filtered fresh air
      Photoperiod: 12 h dark/12 h light
   Acclimation period: 6 days
   Study duration: Approximately 4 months
   In-life dates: 5/5/98-9/3/98

B. PROCEDURES AND STUDY DESIGN

1. Mating procedure: Following acclimation, males and females (1 male/1 female) were cohabited for a maximum of seven days and copulation was confirmed by the presence of a vaginal plug or sperm in a vaginal smear. The day copulation was confirmed was designated as gestation day (GD) 0.

2. Study schedule: P females that delivered a litter were administered the test substance continuously in the diet from GD 6 until lactation day (LD) 11. P females that did not deliver a litter were administered the test substance from GD 6 through GD 24.

3. Animal assignment: The animals were randomly assigned (stratified by body weight) to test groups as shown in Table 1.

Table 1. Animal assignment [a]

Test Group	Nominal Dose (ppm)	Actual Dose (ppm)	Achieved Dose (mg/kg/day) GDs 6-21	Achieved Dose (mg/kg/day) LDs 1-12	# of Females
Control	0	0	0	0	25
Low	100	107	8.8	16.3	25
Mid	300	266	22.0	41.3	25
High	1000	876	65.0	125.4	25

a Data were obtained from the study report Table B1, pages 64, 122-123.

4. Dose selection rationale: Dose levels were selected based on the results of a two-generation reproduction study in Wistar rats. Animals (25/sex/dose) were administered the test substance in the diet at concentrations of 0, 100, 300, or 1000 ppm. At 1000 ppm, hair loss was observed (P females) as well as decreased food consumption (P males), body weight gains (P and F1 males and females), litter size, birth weight, and pup survival to day 5. No treatment-related effects were observed at 100 or 300 ppm.

   Based on the results of this study, the dose levels shown in Table 1 were selected for this developmental neurotoxicity study in rats.

5. Dosage preparation and analysis: Corn oil was used as the vehicle for the test substance at 1% (by weight) of the diet. No further information concerning the method or frequency of preparation of the test diets was provided; however, it was stated that the dietary admixtures were provided to the testing lab by the sponsor and were stored frozen (-20ºC). Aliquots for weekly use were stored at room temperature. Homogeneity and stability were determined using 100 and 1600 ppm samples stored at room temperature for 14 days or in the freezer for 36 days (assumed based on the availability of results

following a 36-day interval). Concentration analyses were performed on all dose preparations.

Results: It was stated that the test substance was homogeneous and stable in the diet for up to 14 days at room temperature and 36 days at -23ºC. Measured concentrations of the dose formulations ranged from 87.6-107% of nominal (only a range was stated in the report). No analytical data were provided. Analytical data (including stability, homogeneity, and concentration verification) and information regarding diet preparation should be provided by sponsor to verify the statements in the study report.

6. Dosage administration: Doses were administered continuously in the diet from GD 6 through LD 11 (dams that delivered a litter) or GD 24 (rats that did not deliver a litter).

C. OBSERVATIONS

1. Parental animals: The P animals were checked for mortality and clinical signs of toxicity at least twice daily. Body weight and food consumption were measured daily during the exposure and post exposure periods beginning on GD 0. During the exposure and post-exposure periods, at approximately the same time each day, rats were examined for signs of autonomic dysfunction (lacrimation, salivation, palpebral closure, prominence of the eye, piloerection, respiration, urination, and defecation) and abnormal posture, movements, and behavior. Observers were unaware of the rat's treatment group. In addition, rats were observed for maternal behavior on lactation days 1, 5, 8, 14, and 22; variations from normal behavior were recorded. P females that did not deliver a litter were sacrificed on presumed GD 25, necropsied, and examined for gross lesions and evidence of pregnancy (uteri were stained with 10% ammonium sulfide and examined for implantation sites). All other P dams were sacrificed on LD 22 and subjected to a gross pathological examination.

2. Litter observations: Pups were evaluated for viability at birth and at least twice daily during the preweaning and postweaning periods. On post-natal day 5, litters were standardized to 10 pups each; when possible 5 pups/sex were retained for each litter. Because of the large number of pup deaths in litters from high dose dams, only 18 litters with at least 9 pups remained at that dose on post-natal day 12. In order to retain 20 litters with at least 9 pups each, two pups from other dams receiving 1000 ppm and two additional pups from control animals were transferred to 1000 ppm dams with smaller surviving litters. The transferred pups were uniquely identified and used for the purpose of balancing litter size only; on postnatal day 22, they were sacrificed and examined by gross necropsy.

Clinical observations were noted daily during the preweaning period and weekly during the postweaning period. Body weights were recorded on PNDs 1, 5, 8, 12, 14, 18, 22, weekly during the postweaning period, and at sacrifice. Food consumption was measured weekly during postweaning. In addition, the following litter observations (X) were made (Table 2a):

Table 2. Litter observations[a]

Observation	Time of observation (lactation day)						
	1	5 [b]	8	12	14	18	22
Number of live pups	X	X	X	X	X	X	X
Pup weight	X	X	X	X	X	X	X
External alterations	X						
Number of dead pups	X	X	X	X	X	X	X
Sex of each pup	X	X	X	X	X	X	X

a Data obtained from the study report Table B12, pages 137-141.
b Before and after standardization (culling).

On post-natal day 12, 20 litters/dose were randomly selected for continuation on study. F1 pups (1/sex/litter, where possible) were assigned to one of 5 subsets for further evaluation (See Table 2b). Physical development was measured by surface righting reflex (evaluated beginning on post-natal day [PND] 1, Subsets 1-5), pinna unfolding (evaluated beginning on PND 2, Subsets 1-5), eye opening (evaluated beginning on PND 12, Subsets 2-5), acoustic startle response (evaluated beginning on PND 13, Subsets 2-5), and pupil constriction (evaluated on PND 21, Subsets 2-5). Evaluations were continued until all pups in the litter met the criterion. Sexual maturation was evaluated in Subsets 2-4 (beginning PNDs 28-39) and was indicated by the age of vaginal patency or preputial separation.

All pups in Subset 1 (78 males and 76 females) were sacrificed on PND 12, examined for gross lesions, and brain weights were recorded. Six pups/sex/dose were processed for neurohistological examinations. All pups in Subset 2 (80 rats/sex) were subjected to a passive avoidance test, beginning on PND 23 to 25. Beginning on PND 59 to 63, the same pups were evaluated using a water-filled M-maze (see below for procedural information for passive avoidance and M-maze). All pups assigned to Subset 3 (80 rats/sex) were subjected to motor activity measurements on PNDs 14, 18, 22, and 62. The same animals were tested for auditory startle habituation on PNDs 23 and 63. All Subset 4 rats (79 males and 80 females) were examined weekly for signs of autonomic dysfunction and abnormal posture, movements, or behavior patterns and were sacrificed on PND 83. Six pups/sex from Subset 4 were randomly selected for fixed brain weights and neurohistological examination (see below). All remaining pups were subjected to a gross necropsy. Subset 5 pups (70 males and 67 females) were used to standardize litter size to 8 pups/litter from PNDs 12 to 22.

Table 2b. Pup Assignment for evaluations.*

Parameter	Subset 1	Subset 2	Subset 3	Subset 4	Subset 5
No. of animals initially assigned (M/F)	78/76	80/80	80/80	79/80	70/67
Physical Developmental Landmarks	X†	X	X	X	X

Sexual Maturation		X	X	X	
Neuropathology (Day 12) Brain weights in all pups Neuropathology in 6/sex/group	X				
Passive Avoidance (Day 23-25)		X			
Watermaze (Day 59-63)		X			
Motor Activity (Days 14, 18, 22, 62)			X		
Auditory Startle Habituation (Days 23, 63)			X		
Weekly detailed clinical observations				X	
Necropsy/Histopathology (Day 83) [6/sex/group]				X	
Necropsy (Day 22)					X

*Approximately 20 animals/sex/group were assigned to each subset. †Surface righting and pinna unfolding only.

Passive Avoidance Testing: Passive avoidance was evaluated in a two-compartment plexiglas chamber. One compartment was brightly lit, while the other was 'dark' and had an electrified grid floor. Training was conducted by placing the rat in the bright compartment; when the rat entered the dark compartment, the door between the compartments was closed and a brief shock was delivered (1 mA for 1 sec). The rat was removed to a holding cage for 30 sec, and the trial was repeated. Training was continued until the rat successfully avoided the dark compartment for 60 sec on two consecutive trials or for a maximum of 15 trials. Latency to enter the dark compartment was recorded for each trial. One week after initial training, each rat was retested as above to evaluate long term retention. Learning and retention were evaluated by comparing the number of trials to criterion and the latency to enter the dark compartment on trials one and two for each session.

Water Maze Testing: Water maze testing was conducted in a water-filled stainless steel modified M-maze. The maze was filled to approximately 9" deep, and water temperature was approximately 21° C. Rats were placed in the base of the maze and required to swim to a goal in one of the two arms (the initial arm chosen on trial 1 was designated as the incorrect goal). Upon reaching the correct goal, the rat was removed from the maze. After a 15-sec interval, the rat was returned to the maze for the next trial. Training continued until rat had made the correct choice in 5 consecutive trials, or for a maximum of 15 trials. Latency to reach the correct goal and the number of errors and trials to criterion were recorded. Testing was repeated one week later, to evaluate long term retention.

Motor Activity Testing: Motor activity was evaluated using a passive infrared sensor, mounted on a stainless steel wire-bottomed cage (solid flooring was used during the pre-weaning period). The number of movements and time spent in movement were recorded for a 90-minute period, during each of 18 5-minute subsessions. Groups were counterbalanced across cage position and sex, with each rat tested in the same cage

position for all test days. Equipment was capable of monitoring a rack containing 32 cages simultaneously. Calibration was carried out at least semi-annually.

Auditory Startle Habituation: Auditory startle habituation was evaluated in a sound-attenuated chamber, with 4 testing units. Each rat was placed on a platform with a force-transducer. After a five minute adaptation period, rats were given 10 blank trials (with no sound stimulus), followed by 50 trials with sound stimulus (30 msec, 120 dBA bursts of noise) at 10 sec intervals, followed by an additional 10 blank trials. Peak response amplitude was calculated by subtracting the average response on blank trials from the response on stimulus trials. Peak response amplitude was averaged over each block of 10 consecutive trials.

Necropsy/Histopathology: All rats were necropsied upon sacrifice. Rats from Subset 1 were sacrificed on lactation day 12; the calvaria was removed after sacrifice and the head was immersed in buffered 10% formalin. Brains were removed and weighed after approximately 48 h in fixative. Brains from 6 pups/sex/group were processed for additional histopathological evaluation.

From Subset 4, six rats/sex/group were selected for neuropathological evaluation on day 83. Selected rats were administered heparin and sodium pentobarbital, and perfused in situ with buffered 10% formalin. Selected tissues were dissected and immersed in neutral buffered 10% formalin (head, vertebral column, and hindlimbs), and later processed for histopathological evaluation.

For day 12 brains (Subset 1), two linear measures were taken (anterior to posterior cerebrum and anterior to posterior cerebellum). Brains were embedded in paraffin, and 6 standardized sections were evaluated. Sections were 7 micrometers thick, and stained with hematoxylin and eosin. Seven additional morphometric measurements were taken (as listed in Table 17); all morphometric measurements were performed with observer unaware of treatment status of tissue. Initially, only high dose and control brains were evaluated (except for linear measurements, which were performed on all brains); because of differences seen in findings from high dose and control animals, mid dose brains were also evaluated morphometrically. Qualitative histopathological evaluations were performed on high dose and control animals only.

For day 83 brains (Subset 4), linear measures were taken as described above. Brains were embedded in paraffin, and 11 standardized sections were evaluated. Spinal cord, Gasserian ganglia, nerve roots, and dorsal root ganglia were also embedded in paraffin. Sections were 5 micrometers thick, and were stained with hematoxylin and eosin, luxol fast blue/cresyl violet, and the Bielschowsky's technique. Peripheral nerve tissues (sciatic nerve, tibial nerve [cross and longitudinal sections]; peroneal and sural nerves [longitudinal sections]) were embedded in glycol methacrylate, sectioned at 2 micrometers, and stained with hematoxylin and eosin, toluidine blue, and the Bielschowsky's technique.

3. Positive controls - A large number of studies and poster summaries were submitted as positive control data. Many of these studies were performed in adult rats, and may not be relevant to procedures used in young rats in the current study. Some of the submitted data were published studies performed in other facilities, with different principal investigators from the current study. The chemicals used in the submitted studies included: acrylamide (30 mg/kg, administered intraperitoneally for 17 days); trimethyltin chloride (8 mg/kg, administered as a single i.p. injection); MK-801 (0.3 mg/kg as a single i.p. injection); carbaryl (100 mg/kg, once by gavage); and DDT (100 mg/kg, once by gavage). These studies are described further in Appendix B.

   The submitted studies and information are not sufficient to validate the testing procedures used in the submitted study.

D. DATA ANALYSIS

1. Statistical analyses: All measured values were subjected to analysis of variance (ANOVA), repeated measures ANOVA, the Kruskal-Wallis Test, or Fisher's Exact test. Details of statistical analyses are provided in the study report, pp. 61-63.

2. Indices:

   Reproductive indices - The following reproductive indices as presented in the study report were calculated for the adults:

   delivering rate (%) = # of females producing at least one live pup/# of pregnant females x 100%

   Offspring viability indices - The following viability indices as presented in the study report were calculated for the litter:

   day 5 viability index (%) = # of live pups at day 5/ # of pups born alive x 100%
   lactation index (%) = # of live pups on day 22/total # of live pups at day 5 (postcull) x 100%

3. Historical control data: Historical control data were provided for the FOB, developmental landmarks, motor activity, passive avoidance, auditory startle, sexual maturation, watermaze, and brain weights and morphometrics.

II. **RESULTS**

A. PARENTAL ANIMALS

1. Mortality and clinical signs: Two high-dose P females died following prolonged gestation, a result of treatment with the test substance. One low-dose female was found dead on lactation day (LD) 17; this death was considered not to be treatment-related because it was not dose-dependent. All other P females survived until scheduled sacrifice.

   Localized alopecia (Table 3) was observed ($p \leq 0.01$) on the undersides of the high-dose P females during gestation (3/25 treated vs. 0/25 controls) and lactation (3/21 treated vs. 0/25 controls). In addition, localized alopecia was observed (p=not statistically significant) on the limbs of high-dose P females during gestation (2/25 treated vs. 0/25 controls) and lactation (5/21 vs. 2/25 controls).

Table 3. Incidence of clinical signs in P females administered tebuconazole from GD 6 to LD 11[a]

Observation	Dose Group (ppm)			
	0	100	300	1000
Presumed Gestation				
Maximum possible incidence (# animals examined)	398[25]	400[25]	403[25]	411[25]
Localized alopecia				
Total	0[0]	0[0]	0[0]	60[5]**
Underside	0[0]	0[0]	0[0]	33[3]**
Limbs	0[0]	0[0]	0[0]	27[2]
Lactation				
Maximum possible incidence (# animals examined)	500[25]	483[24]	488[24]	452[21]
Localized alopecia				
Total	34[2]	0[0]	14[2]	133[7]**[b]
Underside	0[0]	0[0]	0[0]	66[3]**
Limbs	34[2]	0[0]	14[2]	74[5]

a Data extracted from the study report Table B2, pages 124-125. Number of affected animals is presented in brackets.

b Data represents those provided in the study report; however, it should be noted that the sum of alopecia on the underside and limbs does not equal what is presented as total alopecia.

** Statistically significant at $p \leq 0.01$

2. Body weight - Body weights and body weight gains for the P females are presented in Tables 4a and 4b. Body weights were slightly decreased ($p \leq 0.01$) in the high-dose P females throughout gestation (↓4-8%) and from LD1-LD13 (↓6-12%). Body weight decreases were no longer significant on LD22. Body weight gains were decreased ($p \leq 0.01$ or 0.05) in the high-dose P females during GDs 6-9 (↓400%), 6-21 (↓22%), and 0-21 (↓16%) and during LDs 1-4 (↓164%), 4-7 (↓55%). Body weight gain was increased during days 7-12 (68%), perhaps due to removal of test material from diets starting on LD 11. In addition, body weight gains were decreased in the low-dose P females during LDs 1-4 (↓154%, $p \leq 0.05$); however, this difference was not dose-dependent and is not considered treatment-related.

Table 4a. Selected mean body weights (g) for P females administered tebuconazole from GD 6 to LD11[a]

Treatment interval (days)	Dose (ppm)			
	0	100	300	1000
Gestation				
0	237.9±10.1	237.8±9.9	239.2±9.5	238.6±10.3
7	274.7±14.0	277.4±11.9	273.3±11.6	262.6±12.5** (↓4)
16	330.7±19.0	330.2±17.2	327.7±14.9	305.3±15.7** (↓8)
21	390.1±28.5	400.8±23.4	396.6±21.9	366.5±23.1** (↓6)
Lactation				
1	287.3±18.8	291.4±16.8	285.1±17.4	269.2±15.2** (↓6)
6	302.8±17.5	298.3±24.9	298.4±17.7	274.1±16.9** (↓9)
10	327.5±22.7	327.7±13.6	325.2±22.1	289.2±19.8** (↓12)
22	339.2±20.8	337.6±22.4	334.6±24.7	329.6±23.4

a Data were obtained from the study report Tables B3 and B5, pages 126-127 and 129-130. Percent difference from controls is listed parenthetically; n= 25 (0 ppm), 24 (100, 300 ppm [0 ppm during day 1 of lactation only]), 23 (1000 ppm during gestation), or 21 (1000 ppm during lactation); for gestation day 21, n=23 (0 ppm), 20 (100 ppm), 22 (300 ppm); for lactation day 22, n=20 for all groups, except that n=19 for 100 ppm group starting day 18.

** Significantly different from controls at p≤0.01

Table 4b. Selected mean body weight gains (g) for P females administered tebuconazole from GD 6 to LD 11[a]

Treatment interval (days)	Dose (ppm)			
	0	100	300	1000
Gestation				
0-6	35.7±8.1	35.4±7.8	32.8±6.4	36.4±7.6
6-9	3.1±10.1	9.2±9.7*	5.1±8.0	-9.3±8.8** (↓400)
18-21	30.3±15.6	38.0±13.2	37.0±8.7	30.9±13.0
6-21	117.6±23.3	127.6±19.9	126.0±15.9	91.5±21.9** (↓22)
0-21	152.6±24.3	162.9±20.2	158.0±17.1	127.9±23.3** (↓16)
Lactation				
1-4	5.6±13.1	-3.0±14.0* (↓154)	1.7±11.6	-3.6±11.4* (↓164)
4-7	17.2±9.0	16.3±11.6	16.0±13.3	7.7±7.6** (↓55)
7-12	25.9±12.1	25.8±19.0	24.5±21.2	43.5±16.7** (↑68)
1-12	48.0±18.7	39.1±14.8	42.2±20.3	47.6±18.1
1-22	49.9±19.2	46.5±22.9	51.2±18.2	60.3± 25.2 (↑21)

a Data were extracted from the study report, Tables B4 and B6, pages 128 and 131. Percent difference from controls is presented parenthetically; n=25 (0 ppm), 24 (100, 300 ppm [0 ppm during day 1 of lactation only]), 23 (1000 ppm during gestation), or 21 (1000 ppm during lactation); for gestation day 21, n=23 (0 ppm), 20 (100 ppm), 22 (300 ppm); for lactation days 1-22, n=20 for all groups except that n=19 for 100 ppm group starting day 18.

* Significantly different from controls at p≤0.05

** Significantly different from controls at p≤0.01

3. Food consumption - Selected food consumption data are presented in Table 5. When compared to concurrent controls, absolute (g/animal/day) food consumption was reduced ($p \leq 0.05$ or 0.01) in the high-dose dams throughout gestation (↓9-23%) except during the GD 0-6 interval, and during the LD intervals 4-7 (↓20%), 7-12 (↓18%), 1-12 (↓18%), and 1-22 (↓9%). Relative (g/kg/day) food consumption (Table 5) was reduced ($p \leq 0.05$ or 0.01) in the high-dose dams during the GD intervals 6-9 (↓20%), 9-12 (↓10%), 12-15 (↓8%), 15-18 (↓6%), 6-21 (↓9%), and 0-21 (↓5%). In addition, relative food consumption was decreased ($p \leq 0.01$) at the high-dose during the LD intervals 4-7 (↓12%), 7-12 (↓8%), and 1-12 (↓9%).

Table 5. Selected mean relative food consumption (g/kg/day) for P females administered tebuconazole from GD 6 to LD 11[a]

Treatment interval (days)	Dose (ppm)			
	0	100	300	1000
Gestation				
0-6	89.0±9.1	90.5±8.2	88.6±6.6	89.1±8.0
6-9	80.2±12.0	84.5±8.9	82.1±11.2	64.0±13.8** (↓20)
9-12	87.1±11.7	88.9±8.7	89.0±9.3	78.3±18.1* (↓10)
12-15	88.6±8.2	86.6±8.2	88.8±9.4	81.8±6.6** (↓8)
15-18	87.6±5.6	87.0±7.3	88.6±5.3	82.4±5.6** (↓6)
6-21	81.3±5.7	82.8±5.4	82.6±5.3	74.2±6.7** (↓9)
0-21	79.4±5.5	80.8±4.6	80.4±4.2	75.7±5.7* (↓5)
Lactation				
1-4	104.2±18.6	96.2±19.6	101.2±12.7	96.9±20.0
4-7	160.2±19.8	148.9±17.5	157.1±15.8	140.5±20.9** (↓12)
7-12	186.5±11.8	184.5±8.9	184.0±12.1	171.2±18.9** (↓8)
1-12	158.2±12.9	152.1±9.8	155.3±8.6	143.2±17.2** (↓9)
1-22	196.2±11.9	190.6±9.3	194.8±8.0	191.7±14.2

a Data were extracted from the study report Tables B8 and B10, pages 133 and 135. Percent difference from controls is listed parenthetically; n=25 (0 ppm), 24 (100, 300 ppm [0 ppm during day 1-4, 4-7, and 1-12 of lactation]), 23 (1000 ppm during gestation, except during day 9-12 interval [n=22]), or 21 (1000 ppm during lactation); for gestation day 21, n=22 (0 ppm), 20 (100 ppm), 22 (300 ppm), 23 (1000 ppm); starting lactation day 11, n=20 for all groups except that n=19 for 100 ppm group starting on day 17 and n=19 for 0 ppm group for the days 1-22 interval.

* Significantly different from controls at $p \leq 0.05$

** Significantly different from controls at $p \leq 0.01$

4. Parental pathology

a) Macroscopic examination: No treatment-related pathological abnormalities were observed in any treated group at necropsy.

b) Microscopic examination: Not done.

5. Reproductive performance: There were two maternal deaths at the high dose, apparently related to prolonged gestation and dystocia (see above). Mean gestation length was slightly increased at the high dose (23.0 days treated vs. 22.5 days controls [↑2%], p≤0.01). There were no other differences of toxicological concern observed in the reproductive performance of the P females (Table 6).

Table 6. Reproductive performance of P females [a]

Observation	Dose (ppm)			
	0	100	300	1000
Delivering rate	100	100	100	91.3
Gestation length (days)	22.5±0.5	22.6±0.5	22.7±0.5	23.0±0.2**
Number of litters	25	24	24	21

a Data extracted from the study report, Table B11, page 136
** Significantly different from controls at p≤0.01

6. Natural delivery data - Natural delivery findings for the reproductive performance of P dams are shown in Table 7. At the high dose, the number of live fetuses/dam was decreased relative to concurrent controls (↓6%, p≤0.01); while the number of dead fetuses/dam was increased relative to concurrent controls (↑200%, p≤0.01). There were no other treatment-related differences in natural delivery observations.

Table 7. Natural delivery observations of the P females administered tebuconazole from GD 6 to LD 11 [a]

Observation	Dose (ppm)			
	0.00	100	300	1000
# Animals Assigned	25	25	25	25
# Animals Pregnant Pregnancy Rate (%) [b]	25 (100)	24 (96)	24 (96)	23 (92)
# Nonpregnant [b]	0	1	1	2
Total # Implantations Implantations/Dam	379 15.2±1.5	365 15.2±1.6	359 15.0±2.1	312 14.8±2.4
Total # Litters Examined	25	24	24	21
Total # Live Fetuses Live Fetuses/Dam	333 13.9±2.4	340 14.2±1.7	340 14.2±2.4	276** 13.1±2.7 (↓6)
Total # Dead Fetuses (Stillborn) Dead Fetuses/Dam Dams with Stillborn pups (%)	2 0.1±0.3 2 (8.0)	2 0.1±0.4 1 (4.2)	2 0.1±0.3 2 (8.3)	7** 0.3±0.7 (↑200) 5 (23.8)
Mean Pup Weight, Day 1 (g)	6.5±0.5	6.6±0.5	6.4±0.4	6.2±0.4
Sex Ratio (% Male)	50.4±13.4	55.2±15.1	49.1±15.7	48.6±14.5

a Data extracted from the study report Tables B11-12, pages 136-141. Percent difference from controls is presented parenthetically.
b Calculated by reviewers.

** Significantly different from controls at p≤0.01.

B. OFFSPRING

1. Viability and clinical signs: There were fewer pups born alive, more stillborn pups, and more pup deaths during the first week after birth in the high dose group than in controls (Table 8). When compared to concurrent controls, changes (p≤0.01) in viability indices were observed at 1000 ppm as follows: increased stillborn index (↑200%); decreased livebirth index (↓6%); and decreased day 5 viability (precull) (↓6%). The number of pup deaths (calculated by reviewers) were increased during days 1-5 (↑229%) and 1-21 (↑243%). No clinical signs of toxicological concern were observed.

Table 8. F_1 generation mean litter size and viability.[a]

Observation	Dose (ppm)			
	0	100	300	1000
Number of litters	25	24	24	21
Mean litter size				
Day 1	13.9±2.4	14.2±1.7	14.2±2.4	13.1±2.7
Day 5[c]	13.6±2.3	14.0±1.6	13.9±2.4	12.0±2.6
Day 5[d]	9.8±0.8	10.0±0.0	10.0±0.0	9.7±0.8
Day 8	9.8±0.8	10.0±0.0	10.0±0.0	9.6±0.9
Day 14	8.0±0.2	8.0±0.0	8.0±0.0	7.8±0.5
Day 22	8.0±0.2	8.0±0.0	8.0±.0.	7.8±0.5
Number deaths[b]				
Days 1-5[c]	7	4	6	23**
Days 1-22	7	4	6	24**
Viability indices (%)				
Stillborn	0.6	0.6	0.6	2.5** (↑200)
Livebirth	99.4	99.4	99.4	97.2**(↓6)
Viability (Day 5) [c]	97.9	98.8	98.2	91.7** (↓6)

a Data extracted from the study report Table B12, pages 137-141.
b Calculated by the reviewers from data contained in this table.
c Before culling
d After culling
** Significantly different from controls at p≤0.01

2. Body weights and body weight gains: Selected body weights and body weight gains for F1 pups are presented in Tables 9a and 9b. Body weights were decreased (p≤0.01) in the high-dose males from PND 5 to 86 (↓7-23%) and in the high-dose females from PND 5 to 72 (↓5-24%). At the mid-dose, body weights were decreased (p≤0.01 or 0.05) in the males from PND 5 to 23 and 72-86 and in the females from PND 5 to 51 (↓3-7% each).

At the low-dose, body weights were decreased (p≤0.01 or 0.05) in the males from PND 5 to 37 (↓3-6%) and in the females from PND 5 to 51 (↓4-7%).

In the males, differences from controls in body weight gains were observed sporadically throughout the study at the high- (↓39-↑8) and mid- (↓4-16%) dose and during only two intervals at the low-dose (↓6-9%). In the females, differences from controls in body weight gains were observed sporadically throughout the study at the high-dose (↓39-↑7%) and during 4 and 5 intervals at the mid- (↓7-19) and low- (↓4-13%) doses, respectively.

Table 9a. Mean F_1 pup body weights (g).[a]

Post-natal Day	Dose (ppm)			
	0	100	300	1000
Males				
5	10.4±0.9	9.9±1.3* (↓5)	10.0±0.9* (↓4)	9.0±1.1** (↓13)
8	16.1±1.3	15.1±1.8** (↓6)	15.0±1.2** (↓7)	12.5±1.6** (↓22)
12	24.7±2.0	23.4±2.2** (↓5)	23.2±1.9** (↓6)	19.1±2.2** (↓23)
22	55.2±5.0	53.4±4.6* (↓3)	53.1±4.4* (↓4)	48.1±4.6** (↓13)
37	172.1±13.9	165.7±12.3*(↓4)	168.1±10.2	154.8±16.1**(↓10)
51	295.1±26.0	291.4±20.3	291.8±17.7	272.7±21.4**(↓8)
58	350.9±29.7	347.5±26.3	345.9±20.4	325.2±25.5** (↓7)
72	434.9±38.2	429.8±32.9	420.5±30.9* (↓3)	397.4±35.9** (↓9)
86	494.0±45.6	491.4±38.3	473.4±38.9* (↓4)	453.9±39.6** (↓8)
Females				
5	10.0±0.9	9.5±1.4** (↓5)	9.5±1.0** (↓5)	8.5±1.2** (↓15)
8	15.4±1.3	14.3±1.8** (↓7)	14.3±1.4** (↓7)	11.8±1.8** (↓23)
12	23.9±2.1	22.2±2.2** (↓7)	22.1±1.8** (↓7)	18.1±2.3** (↓24)
22	52.8±4.8	50.7±4.4* (↓4)	50.9±4.5* (↓4)	46.0±4.7** (↓13)
37	145.1±11.3	139.5±9.1** (↓4)	140.8±9.7* (↓3)	130.8±11.6** (↓10)
52	206.5±17.4	199.0±16.0*(↓4)	198.9±18.4*(↓4)	191.6±16.7**(↓7)
58	229.2±18.6	222.5±18.0	225.8±19.0	214.5±19.1** (↓6)
72	260.5±22.4	252.7±22.2	254.9±22.8	246.6±24.5** (↓5)
86	281.1±23.2	269.3±23.4	277.3±26.7	267.1±30.8

a Data obtained from the study report Tables C3 and C5, pages 294-295 and 298-299; includes weights of pups selected for continuation on study only. Percent difference from controls is listed parenthetically; n = 76-80 (days 5-12), n=56-60 (days 14-79), n=38-40 (day 86). *Statistically significant at p≤0.05;**Statistically significant at p≤0.01

Table 9b. Selected F_1 pup mean body weight gains (g).[a]

Post-natal Day	Dose (ppm)			
	0	100	300	1000
Males				

5-8	5.7±1.2	5.2±1.1** (↓9)	5.0±0.7** (↓12)	3.5±0.8** (↓39)
8-12	8.6±1.2	8.3±0.9	8.2±1.3	6.6±0.9** (↓23)
5-12	14.3±1.9	13.4±1.6** (↓6)	13.2±1.5** (↓8)	10.2±1.4** (↓29)
37-44	64.7±8.2	65.2±7.2	63.9±5.8	60.7±9.3* (↓6)
65-72	38.2±9.0	38.0±8.5	32.2±10.5** (↓16)	30.2±15.0** (↓21)
79-86	30.4±7.0	29.7±7.6	25.7±6.8** (↓15)	24.9±11.8* (↓18)
5-86	483.7±45.4	481.6±38.0	463.5±38.6* (↓4)	444.9±39.1** (↓8)
Females				
5-8	5.4±0.9	4.7±1.1** (↓13)	4.8±0.8** (↓11)	3.3±0.9** (↓39)
8-12	8.4±1.1	8.0±0.8* (↓5)	7.8±1.2** (↓7)	6.4±1.0** (↓24)
23-30	43.1±4.3	41.2±3.7* (↓4)	41.7±4.0	39.0±5.1** (↓10)
30-37	46.3±5.1	45.2±4.3	46.0±4.3	43.9±5.2** (↓5)
51-58	22.7±6.6	23.5±7.1	26.9±9.8* (↑19)	22.9±7.0
5-86	271.2±22.8	259.8±23.3	267.8±26.6	258.6±30.5

a Data obtained from the study report Tables C4 and C6, pages 296-297 and 300-301. Percent difference from controls is listed parenthetically; n = 76-80 (days 5-12), n=56-60 (days 14-79), n=38-40 (days 80-86).
* Statistically significant at p≤0.05; **Statistically significant at p≤0.01

Food consumption: Food consumption, measured from days 23-86 for animals in subsets 2-4, (g/day) was consistently decreased at the high dose for both males and females, ranging from 3-9% below control levels for males, 4-10% below control levels for females. Relative food consumption (g/kg/day) was consistently increased for high dose males and females, ranging from 3-7% above controls for males, 4-8% above controls for females. No reliable effects on food consumption were seen in the low and mid dose groups.

3. Offspring developmental landmarks: Pinna unfolding was delayed (p≤0.01) in the mid- (↑16%) and high- (↑19%) dose pups relative to concurrent controls (Table 10). No other treatment-related differences in developmental landmarks were observed.

Table 10. Offspring developmental landmark data (days) [a]

Observation	Dose (ppm)			
	0	100	300	1000
Surface righting reflex	2.7±1.5	3.3±1.7	3.2±1.8	2.6±1.8
Pinna unfolding	3.2±0.5	3.3±0.5	3.7±0.5** (↑16)	3.8±0.5** (↑19)
Eye opening	14.6±0.7	14.8±0.8	14.6±0.5	15.0±0.4
Acoustic startle response	13.0±0.2	13.2±0.4	13.0±0.2	13.2±0.4
Pupil constriction	21±0.0	21±0.0	21±0.0	21±0.0

a Data obtained from the study report, Table B14, pages 143-145. Percent difference from controls is listed parenthetically; n=20-25.
** Significantly different from controls at p≤0.01.

Sexual maturation: A slight delay in vaginal patency (33.2 days treated vs. 31.6 days controls [↑5%], p≤0.01) was observed in the high dose F_1 females (Table 11). No differences in preputial separation were observed between treated and control F_1 males.

Table 11. Preputial separation or vaginal patency (days) in F_1 generation males or females.[a]

Parameter	Dose (ppm)			
	0	100	300	1000
Preputial separation - Males	45.4±1.3	45.8±1.3	45.4±1.6	45.7±1.7
Vaginal patency - Females	31.6±2.0	32.0±1.9	32.1±2.0	33.2±1.6** (↑5)

a Data extracted from the study report Table C11, page 306. Percent difference from controls is listed parenthetically; n=56-60.
** Significantly different from controls at p≤0.01

4. Offspring neurotoxicological tests:

a) Passive avoidance: No treatment-related differences were detected in performance on the passive avoidance test for learning, short-term retention, long-term retention, or response inhibition (see Table 12). Increased latency in trial 2 was observed in the 100 ppm males (↑94%, p≤0.05); however, this difference was not dose-dependent and considered not to be treatment-related.

Table 12. Passive Avoidance performance in F1 pups (mean±standard deviation).[a]

Parameter	Dose (ppm)			
	0	100	300	1000
Males				
Session 1				
Trials to Criterion	5.8±3.3	4.6±1.5	5.2±1.4	5.1±1.6
Latency (sec.)				
Trial 1	8.4±4.3	7.5±4.7	6.4±3.5	7.0±6.0
Trial 2	17.4±13.8	33.7±19.7*	13.7±10.7	22.5±18.6
Failed to Learn	2	0	0	0
Session 2				
Trials to Criterion	3.4±2.9	2.8±0.6	2.9±0.8	2.6±0.6
Latency Trial 1 (sec.)	29.8±21.6	31.8±21.6	28.1±23.4	36.9±22.8
Females				

Session 1				
Trials to Criterion	5.2±2.1	4.6±0.8	4.7±0.8	5.4±2.2
Latency (sec.)				
Trial 1	9.0±5.2	8.8±4.3	11.4±12.4	8.7±5.5
Trial 2	20.8±16.2	20.3±11.2	20.4±13.6	24.5±17.7
Failed to Learn	0	0	0	0
Session 2				
Trials to Criterion	2.7±0.6	3.6±2.8	2.8±0.7	3.6±3.0
Latency Trial 1 (sec.)	34.2±24.1	28.2±20.6	35.6±21.9	30.8±22.5

a Data obtained from the study report Table E1, pages 439; n=19-20. *=p<0.05 . Values represent mean±s.d.

b) Watermaze: No differences in watermaze performance were observed in any treated group (see Table 13).

Table 13. Water maze performance in F1 adults (mean±standard deviation).[a]

Parameter	Dose (ppm)			
	0	100	300	1000
Males				
Session 1				
Trials to Criterion	8.9±3.1	9.2±3.1	8.2±2.1	10.0±2.7
Errors per Trial	0.38±0.24	0.40±0.20	0.37±0.22	0.42±0.18
Latency Trial 2 (sec.)	17.3±12.5	14.9±11.2	14.8±8.3	13.5±5.3
Failed to Learn	0	1	0	0
Session 2				
Trials to Criterion	7.0±2.9	6.3±2.5	7.9±3.6	6.9±2.9
Errors per Trial	0.13±0.17	0.07±0.11	0.13±0.16	0.13±0.19
Latency Trial 1 (sec.)	12.0±10.4	8.0±4.4	7.8±4.8	11.0±6.5
Females				
Session 1				
Trials to Criterion	9.2±2.4	9.7±3.2	9.0±2.2	9.2±2.7
Errors per Trial	0.38±0.18	0.40±0.22	0.49±0.24	0.38±0.15
Latency Trial 2 (sec.)	12.5±7.6	14.5±7.6	13.8±8.0	16.6±10.6
Failed to Learn	0	3	1	2
Session 2				
Trials to Criterion	6.6±2.4	5.4±0.9	9.2±4.4	6.6±1.8
Errors per Trial	0.12±0.12	0.06±0.14	0.16±0.18	0.12±0.12
Latency Trial 1 (sec.)	10.0±5.1	9.1±5.7	9.8±7.8	9.2±5.1

a Data obtained from the study report Table E2, page 440; n=19- 20. Values for rats who failed to learn during session 1 were not included in means for session 2. *=p<0.05 . Values represent mean±s.d.

c) Motor activity: On day 14, both low and high dose males and females showed decreases in motor activity; mid-dose males showed smaller decreases (see Table 14). Decreases in motor activity in females at the low and high dose lacked statistical significance (14 and 24%, respectively), but were consistent with the significant decreases in males (35% and 43%, p<0.01). On day 18, low dose males still showed significantly less activity than control males (28%, p<0.05). On day 22, high dose males showed a significant increase (39%, p<0.05). No difference in motor activity among treatment groups was seen on day 62, for either sex.

Differences in motor activity during the five minute intervals were also observed on days 14, 18, and 22 (more commonly in males); most of these differences occurred in groups that showed significant differences in total activity on the same days. For example, on day 14, there were statistically significant decreases in total activity for low and high dose males; examination of individual subsession activity for those days revealed corresponding statistically significant decreases in activity during blocks 4, 5, 8, and 14 in low and high dose males, with additional blocks showing significant decreases at the high dose only (complete motor activity data are presented in Appendix A).

Although there was no reliable dose-response in the motor activity changes seen on day 14 in treated males (or in the decrease seen in low dose males on day 18), similar decreases in activity (of smaller magnitude) were seen in low and high dose females on day 14. Examination of the subsession data, in particular for low dose males, revealed that the decrease in activity was very consistent across the entire 90-minute session. Although the decrease in activity was not statistically significant in females, the magnitude of the difference was sufficiently large (in males) and consistent (across sex and time points) that these effects are considered treatment-related at the low dose in both sexes.

We also note that there was a large degree of variability in the motor activity data, both within the current study and in the submitted historical control data (see Table 14).

Table 14. Total motor activity (number of movements) in F1 pups (mean±standard deviation).[a]

Post-natal Day	Dose (ppm)				
	0	100	300	1000	Historical Controls
Males					
14	784.0±299.7	508.8**±293.7 (↓35)	685.6±269.8 (↓13)	447.6**±227.8 (↓43)	244.0-784.0

18	934.8±320.6	673.6*±380.0 (↓28)	1004.6±195.7	956.0±322.3	NA
22	610.2±357.3	646.2±222.0	645.0±258.2	850.5* ±280.3 (↑39)	314.2-636.4
62	982.8±207.0	877.0±216.5	859.1±209.4	952.2±273.9	563.0-982.8
Females					
14	559.2±337.0	483.2±263.3 (↓14)	610.8±263.6	423.4±183.3 (↓24)	228.4-737.9
18	798.9±318.6	860.2±308.5	867.7±266.0	918.2±349.8 (↑15)	343.3-932.2
22	618.6±284.5	608.0±332.4	617.8±214.6	738.3±277.1 (↑19)	228.9-684.8
62	909.9±185.2	910.5±240.3	899.4±191.6	926.9±211.2	634.6-961.8

a Data obtained from the study report Table F1, pages 468-483; n=19 or 20. Percent difference from controls is listed parenthetically; n=19-20.
* Statistically significant at p≤0.05
** Statistically significant at p≤0.01
NA Data not provided

d) Auditory startle response: Data for auditory startle habituation are presented in table 15 (below). Only data for amplitude were provided; latency data were not submitted. Although there were no statistically significant differences among groups, there was a dose-related decrease in the response amplitude in all treated females on day 23 (a similar decrease was seen in high dose males on this day), and a dose-related increase in response amplitude in all treated males on day 63 (no similar effect was seen in day 63 females; in contrast, a slight decrease in response amplitude was seen at the high dose). It is likely that the effects seen in males on day 63 and in females on day 23 are treatment-related.

Table 15. Auditory startle habituation in F1 rats (mean±standard deviation).[a]

Parameter	Dose (ppm)			
	0	100	300	1000
Males				
Day 23				
Block 1	15.1±6.8	16.0±11.5	14.3±7.4	12.2±7.4
Block 2	8.9±4.8	11.4±10.4	10.2±5.3	8.8±5.6
Block 3	10.5±8.6	11.5±12.8	10.8±7.2	7.3±4.2
Block 4	10.2±9.3	10.2±12.5	8.8±6.4	10.2±8.9
Block 5	13.0±10.1	9.9±9.0	9.5±5.9	11.0±9.3
Mean	11.5±6.4	11.8±10.7	10.7±5.0	9.9±6.0 (↓14%)
Day 63				
Block 1	95.0±62.3	105.1±69.6	110.1±89.0	130.4±118.1
Block 2	55.8±52.2	62.2±55.8	71.3±54.3	112.9±125.6

Block 3	39.4±30.9	48.7±53.0	45.2±39.1	77.8±106.6
Block 4	31.6±19.8	45.0±48.5	34.5±26.8	57.3±75.0
Block 5	32.0±21.3	33.6±33.5	38.0±24.3	55.2±66.0
Mean	50.8±33.1	58.9±49.2 (↑16%)	59.8±40.5 (↑18%)	86.7±94.8 (↑71%)
Females				
Day 23				
Block 1	17.4±9.5	15.4±11.4	12.4±6.9	10.8±6.3
Block 2	12.4±6.6	12.2±10.9	9.3±7.1	7.8±5.4
Block 3	11.7±7.5	12.6±12.4	9.3±7.3	7.2±5.4
Block 4	11.1±6.8	8.8±8.0	8.2±6.6	7.9±5.5
Block 5	9.7±6.7	8.2±6.9	7.0±5.6	8.1±7.0
Mean	12.5±6.2	11.4±9.2 (↓9%)	9.3±5.5 (↓26%)	8.4±4.5 (↓33%)
Day 63				
Block 1	56.4±38.8	54.4±32.9	54.2±31.9	46.2±24.3
Block 2	31.8±32.2	27.2±20.4	33.7±31.4	23.3±15.8
Block 3	25.2±20.4	22.1±20.6	23.1±22.0	17.7±14.5
Block 4	16.7±16.2	19.4±12.0	23.0±18.4	16.8±13.4
Block 5	17.9±15.0	19.6±12.2	20.4±19.0	14.1±12.7
Mean	29.6±20.4	28.5±17.0	30.9±20.2	23.6±12.7 (↓20%)

a Data obtained from the study report Table F2, pages 484-485; n=18-20. *=$p<0.05$. Values represent mean±s.d of response amplitude (g).

5. Offspring postmortem results:

   a) Necropsy: No treatment-related gross pathological findings were noted in Subsets 1, 2, 3, or 4. Only gross lesions were examined histopathologically; the most common finding was kidney changes, most notably dilation of the pelvis, which was seen most frequently in control males.

   b) Brain weights: Body weights (Table 16) were decreased ($p\leq0.01$) in the day 12 (Subset 1) high-dose males and females (↓23-27%) and low- and mid-dose females (↓8-10%). Absolute brain weights were decreased ($p\leq0.01$ or 0.05) in the high-dose males (↓10-15%) and females (↓10-16%) on days 12 and 83, the day 12 low-dose males and females (↓4% each), and the day 12 mid-dose females (↓4%).

   In spite of the lack of a dose relationship between the 100 and 300 ppm groups, the decrease in brain weight on day 12 (Subset 1) is found in both sexes, and is of similar magnitude across sexes. A dose-related decrease in brain weight persisted in both

sexes at day 83, although the magnitude of the decrease was smaller than on day 12 (the low and mid-dose differences from control were no longer statistically significant at day 83). The differences in absolute brain weight are considered treatment-related at all dose levels.

Table 16. Absolute and relative brain weights in F1 pups.[a]

Weight (g)	Dose (ppm)			
	0	100	300	1000
Males				
Day 12 (Subset 1)				
Terminal body weight	24.8±2.3	23.8±2.1 (↓4)	23.7±2.2 (↓4)	19.0±2.2** (↓23)
Absolute brain weight	1.359±0.060	1.301±0.061* (↓4)	1.317±0.061 (↓3)	1.153±0.089** (↓15)
Relative brain weight	5.526±0.455	5.501±0.351	5.590±0.440	6.094±0.497** (↑10)
Day 83 (Subset 4)				
Terminal body weight	510.7±37.8	483.5±52.4 (↓5)	457.3±32.6 (↓10)	454.7±31.6 (↓11)
Absolute brain weight	2.412±0.082	2.340±0.086 (↓3)	2.300±0.120 (↓5)	2.172±0.094** (↓10)
Relative brain weight	0.475±0.036	0.488±0.042	0.505±0.062	0.477±0.025
Females				
Day 12 (Subset 1)				
Terminal body weight	24.4±2.3	22.4±2.4** (↓8)	21.9±1.7** (↓10)	17.8±2.3** (↓27)
Absolute brain weight	1.325±0.061	1.267±0.070* (↓4)	1.273±0.057* (↓4)	1.115±0.101** (↓16)
Relative brain weight	5.466±0.437	5.706±0.426	5.825±0.424* (↑7)	6.302±0.430** (↑15)
Day 83 (Subset 4)				
Terminal body weight	271.0±25.1	274.7±35.0	265.3±25.2 (↓2)	261.7±12.5 (↓3)
Absolute brain weight	2.115±0.068	2.072±0.087 (↓2)	2.071±0.098 (↓2)	1.970±0.086* (↓7)
Relative brain weight	0.782±0.051	0.763±0.102	0.783±0.050	0.752±0.042

a Data obtained from the study report Tables D3-D4 and G3-G4, pages 420-421 and 643-644; n=6 (day 83) or 19-20 (day 11). Percent difference from controls is listed parenthetically.
* Statistically different from controls at p≤0.05
** Statistically different from controls at p≤0.01

c) Neuropathology: No histopathological lesions were found in the brains of animals from the control or high dose group following sacrifice on day 12. The lesions found in animals examined following sacrifice on day 83 are listed in Table 17. There appears to be an increase in incidence of peripheral nerve fiber degeneration among high dose males (intermediate dose groups were not evaluated); similar effects were not seen in females. In addition, hydrocephalus was detected in one high dose male. This could be a spontaneous finding, unrelated to test material. However, it should be noted that treatment-related central nervous system malformations, including hydrocephalus, have been seen in developmental studies with this chemical, so it is also possible that the hydrocephalus may be related to treatment with tebuconazole.

Table 17. Incidence of neuropathological findings on day 83.

	Treatment Group			
	Male		Female	
Lesion	Control	High Dose	Control	High Dose
Sciatic Nerve -nerve fiber degeneration	0	1 (#9463, MF)	1 (#9853)	0
Peroneal Nerve -nerve fiber degeneration	0	1 (#9408)	0	0
Tibial Nerve -myelin sheath swelling -nerve fiber degeneration	1 0	0 2 (#9463, 9478)	0 0	0 0
Axonal degeneration -some peripheral nerve	0	3	1	0
Hydrocephalus	0	1 (#9438, mild)	0	0
Dilation of the aqueduct (midbrain)	0	0	1 (#9856)	1(#9810, mild)

N=6 for all groups. All lesions were minimal unless otherwise specified. MF=multifocal; all other lesions were focal. Numbers in parentheses represent animal number. Data were extracted from individual animal pathology data tables, pp. 827-843.

d) Morphometric measurements: Morphometric measurements are presented in Table 18, below. Statistically significant differences were found for several measurements between treated (mostly high dose) and control dose groups, including decreased (p≤0.01) thickness of the cerebellum in the high-dose males and females in Subsets 1 (day 12, ↓10-14%) and 4 (day 83, ↓7-9%). In addition, an increased thickness of the germinal layer of the cerebellar cortex was observed in the Subset 1 high-dose males (↑23%, p≤0.01). Other differences in brain morphometry included decreased (p≤0.05)

thickness of the frontal cortex (↓8%) and hippocampal gyrus (↓9%). The anterior/posterior measurement of the cerebrum was significantly smaller than the corresponding control measurements for all treated groups of males on day 83, and for all treated females on day 12. Measurements were also smaller for all treated males on day 12, but the difference was statistically significant only at the high dose.

It is likely that the decrease in anterior/posterior cerebrum measurement at all doses, as well as some of the other changes in morphometric measurements at the high dose, are treatment-related. These differences are consistent with the decrease in brain weight seen at all doses (see above). Failure to demonstrate strict dose-relationships among treatment groups is likely related to the small number of animals evaluated (6/sex). Statistically significant changes in other morphometric measurements at the mid-dose are not considered treatment-related, since there is no apparent consistency in the findings compared across groups and/or sexes, and examination of individual data failed to indicate a clear difference in the range of values for a given measurement between mid dose and control groups.

It should be noted that the mean brain weights for day 12 males selected for morphometric evaluation (shown in Table 18) are not consistent with those for the entire group of Subset 1 (day 12) control males (shown in Table 16, above). Specifically, the mean brain weight for the six control males evaluated morphometrically (1.305 g), was smaller than the corresponding mean brain weight determined for the twenty control males in Subset 1 (1.359 g) [when individual brain weight data are examined, it can be seen that the 4 control males with the lowest brain weights were all selected for histopathological evaluation; if brain weights are ranked from lowest (1) to highest (20), the mean rank of the six selected brains is 4.75, compared to 13.0 for the remaining fourteen (unselected) brains]. Similarly, the mean brain weight for mid-dose males in the morphometric group (1.346 g) was higher than the mean brain weight for mid-dose males in Subset 1 (1.317 g). The brains used for morphometric evaluation represent a subset of the 20 brains/sex/group used for determination of the means presented in Table 16. Since a larger number of subjects are included in the Table 16 data, the values in Table 16 are considered more reliable. It appears that the brains evaluated for morphometrics were not entirely representative of the treatment group. If the control brains chosen for morphometric analysis had been more representative, it is possible that larger treatment-related differences in morphometric measures would have been seen.

Table 18. Selected brain morphometry data for F1 pups.[a]

Morphometric parameter, thickness (µm unless otherwise stated)	Dose (ppm)			
	0	100	300	1000
Males				
Day 12				
Brain weight[#] (g)	1.305±0.035	1.307±0.047	1.346±0.046	1.151±0.058**
Ant/Post Cerebrum (mm)	12.63±0.19	12.40±0.20	12.45±0.32	12.18±0.22**
Ant/Post Cerebellum (mm)	5.53±0.43	5.38±0.33	5.32±.025	5.05±0.31

Frontal Cortex	1488.0±106.3	NA	1484.0±66.9	1368.0±26.3*
Parietal Cortex	1520±65.6	NA	1608±85.9*	1380±54.2**
Caudate Putamen	2304±145.6	NA	2488±178.1	2048±178.7*
Corpus Callosum	286.3±26.8	NA	257.5±30.1	263.8±72.5
Hippocampal Gyrus	984±56.8	NA	1052±73.5	932.0±41.3
Cerebellum	3376±134.6	NA	3440±222.4	2896±49.6** (↓14)
External germinal layer of cerebellar cortex	30.3±3.9	NA	34.5±2.0	37.2±4.4** (↑23)
Day 83				
Ant/Post Cerebrum (mm)	16.73±0.36	16.22±0.26*	16.02±0.40**	16.30±0.33*
Ant/Post Cerebellum (mm)	7.60±0.55	7.88±0.17	7.35±0.48	7.12±0.37
Frontal Cortex	1836±86.9	NA	1812.0±89.5	1808.0±82.7
Parietal Cortex	1868±41.3	NA	1748±79.5*	1848±108.4
Caudate Putamen	3624±207.6	NA	3280.0±112.2**	3464.0±140.5
Corpus Collosum	285.0±13.2	NA	304.0±22.4	275.3±51.1
Hippocampal Gyrus	1640.0±69.0	NA	1624.0±117.2	1644.0±90.8
Cerebellum	5088±160.6	NA	5280.0±187.1	4736±165.4** (↓7)
Females				
Day 12				
Brain weight[#] (g)	1.326±0.068	1.248±0.061	1.301±0.040	1.140±0.082**
Ant/Post Cerebrum (mm)	12.98±0.17	12.15±0.34**	12.48±0.17**	12.32±0.35**
Ant/Post Cerebellum (mm)	5.50±0.33	5.4±0.42	5.28±0.21	4.97±0.39
Frontal Cortex	1616.0±170.8	NA	1480.0±85.4	1464±116.6
Parietal Cortex	1616.0±91.9	NA	1528.0±49.6	1504.0±101.4
Caudate Putamen	2384.0±170.8	NA	2256.0±52.6	2240.0±99.1
Corpus Collosum	320.2±50.6	NA	272.0±29.6	276.8±40.7
Hippocampal Gyrus	1024.0±69.0	NA	984.0±54.7	932.0±51.3*
Cerebellum	3472±170.8	NA	3320±93.2	3120±221.0** (↓10)
External germinal layer of cerebellar cortex	38.0±7.1	NA	36.8±2.4	40.5±6.7
Day 83				
Ant/Post Cerebrum (mm)	15.88±0.42	15.77±0.31	15.60±0.33	15.88±0.38
Ant/Post Cerebellum (mm)	7.38±0.17	7.20±0.35	7.43±0.31	7.10±0.24
Frontal Cortex	1752±50.3	NA	1764±58.3	1772±76.5
Parietal Cortex	1824±72.8	NA	1736±79.8	1780±55.6
Caudate Putamen	3264±151.8	NA	3240±26.3	3360±221.0
Corpus Collosum	267.2±26.9	NA	264.0±16.9	254.3±18.7
Hippocampal Gyrus	1568±69.0	NA	1556±124.6	1548±98.1
Cerebellum	4960±84.1	NA	5064±181.5	4536±131.4** (↓9)

a Data obtained from the study report Appendices L and M, pages 775-778 and 810-813; n=6. *=p<0.05, **=p<0.01 vs. controls. Percent difference from controls is listed parenthetically; [#]brain weight included here is for the six animals subjected to morphometric evaluation only (brain weight at day 11 in Table 14 includes 19-20 animals/sex/group, the six included here are a subset selected for morphometric and histopathological evaluation).

III. **DISCUSSION**

A. INVESTIGATORS' CONCLUSIONS: Maternal toxicity at 1000 ppm was characterized by mortality, decreased body weight and food consumption, and prolonged gestation.

Offspring toxicity at 1000 ppm was characterized by mortality, reduction in body weight and body weight gains, decreased absolute brain weight, decreased cerebellar thickness, and a delay in vaginal patency. The LOAEL for offspring and dams is 1000 ppm and the NOAEL in offspring and dams is 300 ppm.

B. REVIEWER'S DISCUSSION: Tebuconazole (96-96.9% a.i.) in corn oil was administered via the diet to pregnant Crl:CD®BR VAF/Plus® (Sprague Dawley) rats (25/dose) from GD 6 to 24 or LD 11 at doses of 0, 100, 300 or 1000 ppm (equivalent to [GD/LD] 0/0, 8.8/16.3, 22.0/41.3, and 65.0/125.4 mg/kg/day). No analytical data were provided. P dams were allowed to deliver naturally. On day 5 postpartum, litters were standardized to a maximum of 10 pups/litter with 5/sex/litter, as described in the methods section. Pups were assigned to one of 5 Subsets and physical development, sexual maturation, and neurotoxicity were evaluated.

1. Maternal toxicity: Maternal toxicity was seen only at the high dose. Maternal systemic/clinical effects included alopecia, decreases in body weight (4-12%), body weight gain, and food consumption. Body weight had recovered to control levels by LD22 (subsequent to the termination of dosing after LD10). There were also several changes in reproductive parameters at the high dose, including increased number of dead fetuses and prolonged gestation. Maternal mortality (2 high dose dams) was seen in association with the prolonged gestation and dystocia.

   The LOAEL for maternal toxicity is 1000 ppm (equivalent to [GD/LD] 65.0/125.4 mg/kg/day) based on decreased body weights, body weight gains, and food consumption, and an increased number of dead fetuses. The NOAEL is 300 ppm (equivalent to [GD/LD] 22.0/41.3 mg/kg/day).

   The NOAEL is 300 ppm (equivalent to 41.3 mg/kg/day).

2. Offspring toxicity: Offspring toxicity was seen at all doses. The most consistent effect was decreased body weight, most notably during early lactation. Although there was no difference in body weight among groups on day 1, body weight for all treated groups was lower than that of control groups starting on day 5; the lower body weight persisted to approximately day 51 in low and mid-dose groups, and throughout the study in the high dose groups. The difference in body weight was supported by decreases in body weight gain; decreases in food consumption were seen in the high dose only (as there was no direct exposure to pups through the food, these decreases in food consumption can not be related to changes in feed palatability).

   In addition to the decrease in body weight, there was a decrease in survival for high dose pups, during postnatal days 1-5. There were also delays in several physical/developmental landmarks; pinna unfolding was delayed at the high and mid-dose, and vaginal patency was delayed in the high dose only.

   Behavioral evaluations also revealed differences from controls across all treated groups, although the differences were not always dose-related. Although there were no apparent

effects on the learning/memory tasks evaluated, there were changes in auditory startle amplitude and motor activity levels. For auditory startle, a dose-related decrease in amplitude was seen at all doses in day 23 females, and in high dose females on day 63. Males also showed a decrease in amplitude in the mid and high dose groups on day 23, but on day 63, there was a dose-related increase in amplitude across all treated male groups. Motor activity findings were less clear-cut; there was a decrease in activity at the low and high doses for males on days 14 and 18, and for low and high dose females on day 14. There was a slight decrease in activity of the mid-dose males on day 14, but no effects were seen in mid dose males on day 18 or in mid dose females on either day. There was also an increase in activity in high dose males on day 22 and high dose females on days 18 and 22; all treated groups demonstrated levels of activity comparable to controls on day 62. Although there was not a consistent pattern of effects across doses, the magnitude of effects in low dose males (35% decrease on day 14, 28% decrease in day 18), and the consistency of the pattern across sexes, provide evidence that the changes seen at the low dose were treatment related.

Decreases in brain weight were also seen in all tebuconazole-treated groups. These differences were statistically significant at the low dose for both males and females on day 12, for the mid-dose females on day 12, and for high dose males and females on days 12 and 63. Similar differences were also found in some other brain measurements, most notably the decrease in anterior/posterior cerebrum measurements. These differences in brain measurements increase the strength of the finding of a decrease in brain weight at all doses. The magnitude of the change was larger in the high dose group (15-16% decrease in brain weight at day 12, compared to a 4% decrease at the low dose), and several differences in morphometric measurements were also seen at that dose.

Taken together, these findings provide strong support for treatment-related findings in the offspring at all doses. These findings were seen in several types of behavioral indices, in body weight, and in brain weight and measurements. Some of the findings appear to be persistent, especially at the high dose.

The LOAEL for offspring toxicity is 100 ppm (equivalent to [GD/LD] 8.8/16.3 mg/kg/day) based on decreases in body weights (3-7%) and body weight gain (4-13%), decreases in brain weight (2-4%) and measurements (3-6%), and decreases in motor activity.

The NOAEL is not determined.

This study is classified as **acceptable/guideline (§83-6[a])** and satisfies the requirement for a developmental neurotoxicity study in rats.

C. STUDY DEFICIENCIES: The following deficiencies were noted, but will not affect the conclusions of the review (requested information should be submitted):

- Information regarding homogeneity, stability, or concentration of test substance in the diet were provided in the text of the study report; however, supporting data were not

submitted. Information regarding diet preparation was also not included in the report. These data should be submitted.

- Additional positive control data need to be submitted, as discussed above and described in Appendix B.

APPENDIX A

Protocol 1702-004: Developmental neurotoxicity study of technical grade Tebuconazole administered orally via diet to Crl:CD(R)BR VAF/Plus(R) presumed pregnant rats (Sponsor's study number: 98-C612-QU)

TABLE F1 (page 1): Motor Activity - Summary - F1 Generation Rats - Subset 3

Maternal dosage Group	I	II	III	IV
Maternal dietary concentration (ppm)	0(carrier)	100	300	1000
Day 14 Postpartum				
Male rats	20	20	20	20
Number of movements				
Block 1	40.9±27.3	29.4±23.7	48.4±24.1	43.0±20.2
Block 2	45.4±28.9	32.2±24.7	49.6±22.4	36.2±20.6
Block 3	52.2±26.1	36.0±23.4	46.2±17.4	33.5±20.1*
Block 4	51.6±22.7	27.0±19.6**	44.2±26.2	30.2±23.8*
Block 5	47.4±24.8	27.8±24.2*	42.6±23.3	27.2±21.6*
Block 6	39.2±31.6	27.0±25.0	37.8±23.9	27.2±22.7
Block 7	41.6±28.8	34.0±27.4	38.9±29.8	24.4±21.0
Block 8	54.8±28.9	32.1±27.1*	35.1±29.9	21.2±18.7**
Block 9	50.6±24.1	32.2±29.9	31.7±26.9	20.9±17.4**
Block 10	39.6±32.3	31.8±25.6	27.9±24.1	24.5±19.0
Block 11	46.1±30.7	30.3±28.6	29.4±26.2	24.8±18.9*
Block 12	36.8±26.9	26.2±28.2	41.7±22.8	26.2±25.9
Block 13	34.8±31.1	20.0±24.1	40.2±25.9	25.0±23.4
Block 14	45.6±36.6	22.2±23.8*	40.5±26.1	17.3±19.3**
Block 15	38.8±30.3	21.9±20.4	33.8±26.1	21.2±22.7
Block 16	33.6±31.8	20.8±19.2	29.4±25.6	18.7±23.1
Block 17	41.4±29.1	28.5±20.4	33.4±26.9	10.6±15.3**
Block 18	43.6±32.2	29.2±27.6	35.0±26.6	15.4±18.2**
Total	784.0±299.7	508.8±298.7**	685.6±269.8	447.6±227.8**

Total = Sum of blocks; each Block consists of a 5 minute period.
* Significantly different from the carrier group value ($p \leq 0.05$).
** Significantly different from the carrier group value ($p \leq 0.01$).

Protocol 1702-004: Developmental neurotoxicity study of technical grade Tebuconazole administered orally via diet to Crl:CD(R)BR VAF/Plus(R) presumed pregnant rats (Sponsor's study number: 98-C612-QU)

TABLE F1 (page 2): Motor Activity - Summary - F1 Generation Rats - Subset 3

Maternal dosage Group	I	II	III	IV
Maternal dietary concentration (ppm)	0(carrier)	100	300	1000
Day 14 Postpartum				
Male rats	20	20	20	20
Time (seconds) spent in movement				
Block 1	38.8±33.8	24.8±28.8	43.7±25.8	46.2±34.9
Block 2	45.0±35.2	28.9±33.4	50.6±27.3	37.3±32.2
Block 3	55.4±37.0	36.4±33.3	50.4±24.5	35.0±32.1
Block 4	57.0±37.4	29.1±32.7	53.2±43.5	36.5±42.9
Block 5	55.0±38.2	28.1±35.8	44.8±35.7	31.6±33.4
Block 6	45.3±46.9	26.6±33.4	44.0±34.8	29.4±37.2
Block 7	50.8±44.0	36.3±37.2	53.2±52.0	29.4±39.7
Block 8	71.4±49.9	37.7±44.3*	45.8±45.5	20.8±31.9**
Block 9	67.0±42.1	37.0±44.8*	38.0±40.3	21.6±24.1**
Block 10	51.5±52.5	34.8±33.1	35.0±41.4	25.8±26.2
Block 11	59.8±47.5	34.8±40.4	32.4±36.2	24.8±24.4*
Block 12	50.8±53.6	29.2±34.7	50.6±39.0	35.3±49.2
Block 13	44.4±51.5	23.8±37.7	51.0±46.2	30.4±40.1
Block 14	60.8±57.4	25.8±36.4*	50.4±39.1	18.2±23.7**
Block 15	51.2±50.7	20.2±25.1*	49.8±46.9	23.2±34.0
Block 16	43.8±57.4	21.6±34.9	36.9±45.5	25.2±46.2
Block 17	55.0±50.9	30.5±31.0	42.3±47.9	10.1±20.0**
Block 18	62.2±58.9	32.6±41.4	49.4±52.0	13.1±22.2**
Total	965.2±510.9	538.1±452.0*	821.6±469.9	493.8±444.5**

Total = Sum of blocks; each Block consists of a 5 minute period.
* Significantly different from the carrier group value ($p \leq 0.05$).
** Significantly different from the carrier group value ($p \leq 0.01$).

Protocol 1702-004: Developmental neurotoxicity study of technical grade Tebuconazole administered orally via diet to Crl:CD(R)BR VAF/Plus(R) presumed pregnant rats (Sponsor's study number: 98-C612-QU)

TABLE F1 (page 3): Motor Activity - Summary - F1 Generation Rats - Subset 3

Maternal dosage Group	I	II	III	IV
Maternal dietary concentration (ppm)	0(carrier)	100	300	1000
Day 14 Postpartum				
Female rats	20	20	20	20
Number of movements				
Block 1	39.7±23.6	29.2±21.4	42.2±25.7	36.6±21.5
Block 2	36.9±21.9	34.2±20.3	40.1±20.4	26.8±20.9
Block 3	44.5±25.3	37.4±27.4	43.0±22.6	29.2±21.4
Block 4	41.1±22.8	37.4±20.8	45.1±20.1	30.6±18.6
Block 5	30.8±26.7	32.6±25.0	34.2±22.4	30.4±20.2
Block 6	35.8±29.0	31.6±22.8	31.8±27.9	29.4±22.8
Block 7	40.0±31.8	32.0±25.7	28.2±22.9	25.8±21.5
Block 8	28.4±27.4	28.6±27.4	30.6±24.0	17.4±18.8
Block 9	26.6±29.5	20.6±24.2	33.2±27.3	17.6±16.1
Block 10	29.0±28.7	22.8±22.6	32.8±22.4	21.1±24.6
Block 11	25.5±25.6	23.6±22.4	30.0±30.3	26.6±23.7
Block 12	28.4±27.1	26.9±25.2	30.4±25.3	23.0±24.9
Block 13	24.2±26.2	26.0±21.0	28.8±24.4	23.0±19.7
Block 14	21.8±25.3	26.3±27.1	27.1±24.7	23.2±23.1
Block 15	30.5±28.7	23.4±16.6	29.8±26.5	19.2±22.9
Block 16	29.8±30.6	17.3±16.5	30.3±26.0	15.4±17.8
Block 17	22.4±24.6	15.0±16.3	39.6±30.2*	13.5±15.9
Block 18	23.8±25.1	18.2±18.9	33.6±24.4	14.6±17.3
Total	559.2±337.0	483.2±263.3	610.8±263.6	423.4±183.3

Total = Sum of blocks; each Block consists of a 5 minute period.

* Significantly different from the carrier group value ($p \leq 0.05$).

Protocol 1702-004: Developmental neurotoxicity study of technical grade Tebuconazole administered orally via diet to Crl:CD(R)BR VAF/Plus(R) presumed pregnant rats (Sponsor's study number: 98-C612-QU)

TABLE F1 (page 4): Motor Activity - Summary - F1 Generation Rats - Subset 3

Maternal dosage Group	I	II	III	IV
Maternal dietary concentration (ppm)	0(carrier)	100	300	1000
Day 14 Postpartum				
Female rats	20	20	20	20
Time (seconds) spent in movement				
Block 1	40.0±33.0	26.1±23.2	48.7±46.8	34.6±33.1
Block 2	37.2±35.3	32.6±28.1	50.8±41.6	25.7±28.3
Block 3	50.6±39.2	38.1±32.1	56.8±43.6	28.3±30.0
Block 4	49.4±37.3	40.0±31.9	61.2±50.2	27.6±26.4
Block 5	36.0±36.2	35.4±38.2	49.8±50.3	31.6±26.5
Block 6	45.5±47.7	31.8±31.9	48.0±57.3	32.8±32.3
Block 7	57.6±58.0	36.2±36.3	40.0±46.9	27.6±30.4
Block 8	41.9±50.8	32.4±35.2	41.1±43.7	18.6±29.1
Block 9	36.4±51.8	25.2±38.4	49.2±50.4	17.2±20.4
Block 10	39.4±51.0	28.9±36.5	43.4±41.9	20.6±30.2
Block 11	37.4±49.1	28.0±37.6	37.2±40.0	25.3±27.9
Block 12	44.9±53.9	31.9±40.2	38.2±41.2	24.0±30.7
Block 13	33.3±44.6	31.8±32.2	42.2±46.7	23.4±25.8
Block 14	33.6±56.6	34.4±43.3	40.9±57.0	25.6±36.8
Block 15	41.4±53.2	28.6±32.7	48.2±58.0	20.6±36.6
Block 16	42.7±53.5	21.3±32.8	44.8±49.4	14.2±23.4
Block 17	26.9±42.3	12.8±18.0	51.0±49.2	10.2±16.6
Block 18	35.3±52.4	20.2±29.2	49.4±49.4	12.4±20.0
Total	729.5±620.8	535.9±445.6	841.3±633.7	420.3±275.1

Total = Sum of blocks; each Block consists of a 5 minute period.

Protocol 1702-004: Developmental neurotoxicity study of technical grade Tebuconazole administered orally via diet to Crl:CD(R)BR VAF/Plus(R) presumed pregnant rats (Sponsor's study number: 98-C612-QU)

TABLE F1 (page 5): Motor Activity - Summary - F1 Generation Rats - Subset 3

Maternal dosage Group	I	II	III	IV
Maternal dietary concentration (ppm)	0(carrier)	100	300	1000
Day 18 Postpartum				
Male rats	20	19a	20	20
Number of movements				
Block 1	65.0±20.3	50.9±24.0	61.6±13.9	50.5±24.3
Block 2	66.8±17.3	54.4±22.3	63.4±14.4	61.0±22.1
Block 3	60.6±15.2	44.4±24.5*	63.4±14.9	62.7±19.0
Block 4	60.8±18.6	44.3±24.8*	64.8±17.1	64.1±11.5
Block 5	60.4±12.1	44.5±25.0*	68.1±15.6	61.2±14.2
Block 6	58.0±20.1	41.0±29.2*	66.6±9.1	60.8±17.8
Block 7	52.6±28.4	43.2±30.2	58.1±16.2	59.8±22.9
Block 8	53.2±27.8	45.8±32.2	58.0±16.5	64.6±22.3
Block 9	50.3±30.8	39.8±36.7	56.6±23.9	51.4±28.6
Block 10	42.7±29.9	34.8±32.1	55.2±22.0	45.4±36.4
Block 11	41.7±28.3	35.0±32.2	55.7±18.2	47.6±32.9
Block 12	48.6±30.0	33.4±32.0	52.6±23.9	48.2±31.0
Block 13	48.4±31.7	36.0±32.5	47.0±27.8	52.6±29.1
Block 14	42.1±28.8	31.5±33.8	53.9±27.9	55.8±26.4
Block 15	48.8±29.5	24.4±31.2*	45.1±30.8	43.4±29.8
Block 16	49.6±30.5	30.3±32.0	48.6±27.1	45.4±31.0
Block 17	42.4±30.0	24.2±28.8	49.4±25.8	39.0±28.5
Block 18	42.6±29.9	15.8±25.5*	36.6±26.9	42.5±32.2
Total	934.8±320.6	673.6±380.0*	1004.6±195.7	956.0±322.3

Total = Sum of blocks; each Block consists of a 5 minute period.

a. Excludes values for rat 9317, which was not continued on study.

* Significantly different from the carrier group value ($p \leq 0.05$).

Protocol 1702-004: Developmental neurotoxicity study of technical grade Tebuconazole administered orally via diet to Crl:CD(R)BR VAF/Plus(R) presumed pregnant rats (Sponsor's study number: 98-C612-QU)

TABLE F1 (page 6): Motor Activity - Summary - F1 Generation Rats - Subset 3

Maternal dosage Group	I	II	III	IV
Maternal dietary concentration (ppm)	0(carrier)	100	300	1000
Day 18 Postpartum				
Male rats	20	19a	20	20
Time (seconds) spent in movement				
Block 1	98.4±40.9	64.3±44.9	94.4±45.1	71.4±55.9
Block 2	107.0±39.8	70.7±41.5*	117.8±48.1	93.7±53.5
Block 3	105.0±46.5	62.7±52.7*	124.5±41.1	96.0±51.0
Block 4	104.6±48.8	61.3±51.1*	122.8±44.0	106.6±37.1
Block 5	100.8±44.8	66.6±50.8	118.3±45.3	95.6±47.2
Block 6	102.8±56.7	57.5±57.7*	123.1±51.6	100.4±43.8
Block 7	87.8±58.9	74.8±66.2	112.8±52.2	90.2±46.8
Block 8	89.4±58.6	74.9±65.7	108.2±42.8	103.4±54.0
Block 9	94.7±71.6	61.8±65.1	113.0±68.0	77.3±48.7
Block 10	80.4±72.3	60.4±66.0	101.5±54.1	74.2±68.0
Block 11	79.4±71.7	63.2±69.5	99.1±49.4	73.0±61.2
Block 12	90.2±70.7	56.3±59.8	95.1±60.9	72.5±55.3
Block 13	88.8±69.4	60.0±64.9	82.6±58.8	80.3±53.6
Block 14	68.5±56.7	64.0±75.1	92.7±57.0	93.0±57.8
Block 15	84.0±56.9	43.2±57.8	77.4±59.8	74.9±57.1
Block 16	91.1±69.2	51.5±63.6	77.7±55.6	76.4±60.6
Block 17	77.9±63.3	36.7±51.0	87.4±54.1	64.2±58.9
Block 18	72.7±62.9	28.7±56.8	68.4±61.0	70.4±67.7
Total	1623.6±844.3	1058.5±831.3	1817.0±643.6	1513.3±724.3

Total = Sum of blocks; each Block consists of a 5 minute period.
a. Excludes values for rat 9317, which was not continued on study.
* Significantly different from the carrier group value ($p \leq 0.05$).

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TABLE F1 (page 7): Motor Activity - Summary - F1 Generation Rats - Subset 3

Maternal dosage Group	I	II	III	IV
Maternal dietary concentration (ppm)	0(carrier)	100	300	1000
Day 18 Postpartum				
Female rats	20	19a	20	20
Number of movements				
Block 1	55.8±20.8	47.7±24.9	61.0±17.4	51.8±27.0
Block 2	59.8±19.0	57.2±26.0	63.0±13.6	64.4±20.1
Block 3	59.2±18.2	57.2±16.1	59.8±14.8	57.8±22.4
Block 4	54.4±18.0	54.5±22.1	63.6±12.0	63.8±20.2
Block 5	56.5±16.1	54.2±22.4	59.9±19.5	62.9±16.1
Block 6	52.6±23.9	59.2±24.0	54.0±21.6	56.4±25.7
Block 7	50.2±23.5	49.6±28.5	54.7±24.8	56.4±24.5
Block 8	52.6±22.2	56.6±23.2	52.9±21.2	56.5±23.4
Block 9	44.9±24.9	52.4±22.2	43.8±28.9	51.8±27.7
Block 10	40.7±31.6	46.4±29.5	39.6±29.0	50.5±28.4
Block 11	35.2±31.3	48.5±30.7	40.6±31.1	50.4±30.2
Block 12	32.8±27.5	41.2±29.8	33.8±25.8	49.1±29.1
Block 13	32.3±31.7	43.8±28.1	41.0±29.7	48.4±29.2
Block 14	31.0±28.5	37.9±29.6	37.1±29.0	46.6±31.2
Block 15	32.7±27.4	37.2±31.0	35.3±30.5	39.2±31.7
Block 16	32.2±29.4	35.9±31.1	39.8±26.9	36.7±30.1
Block 17	37.7±30.6	36.5±28.8	41.6±28.1	36.2±27.8
Block 18	38.1±35.4	44.3±29.8	46.2±31.3	39.3±28.8
Total	798.9±318.6	860.2±308.5	867.7±266.0	918.2±349.8

Total = Sum of blocks; each Block consists of a 5 minute period.
a. Excludes values for rat 9317, which was not continued on study.

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TABLE F1 (page 8): Motor Activity - Summary - F1 Generation Rats - Subset 3

Maternal dosage Group	I	II	III	IV
Maternal dietary concentration (ppm)	0(carrier)	100	300	1000
Day 18 Postpartum				
Female rats	20	19a	20	20
Time (seconds) spent in movement				
Block 1	92.1±54.3	83.3±52.4	91.2±41.5	69.6±46.5
Block 2	98.2±40.3	86.5±53.6	101.6±31.4	96.6±41.2
Block 3	94.8±39.0	93.8±47.7	101.8±38.5	87.3±39.2
Block 4	90.8±47.3	101.0±54.3	106.8±26.9	107.3±44.8
Block 5	95.0±39.8	94.3±50.2	95.5±38.0	103.9±38.5
Block 6	84.2±42.4	95.5±46.7	84.8±48.3	95.5±49.5
Block 7	82.6±51.0	83.2±55.5	94.6±53.9	92.6±46.9
Block 8	94.3±46.2	96.9±56.3	88.3±48.0	94.9±48.3
Block 9	72.8±46.9	93.5±62.6	75.6±58.6	90.8±56.8
Block 10	71.3±61.0	86.4±67.6	67.0±60.6	92.4±59.4
Block 11	58.0±54.1	89.6±70.2	69.1±61.4	85.8±55.7
Block 12	53.9±50.3	69.3±60.3	57.8±53.3	93.0±58.4
Block 13	54.5±60.6	75.7±58.7	68.4±60.2	79.8±52.0
Block 14	49.8±51.4	66.8±60.0	61.6±52.4	80.5±60.6
Block 15	50.5±47.6	66.2±66.2	55.3±56.0	70.2±65.1
Block 16	56.8±58.2	57.0±53.2	68.5±51.2	71.9±65.2
Block 17	63.2±56.7	62.0±57.6	72.1±56.0	68.5±63.4
Block 18	60.4±59.5	79.0±65.3	76.6±57.1	71.8±63.1
Total	1323.3±650.4	1480.2±764.5	1436.8±565.0	1552.5±731.6

Total = Sum of blocks; each Block consists of a 5 minute period.
a. Excludes values for rat 9317, which was not continued on study.

TABLE F1 (page 9): Motor Activity - Summary - F1 Generation Rats - Subset 3

Maternal dosage Group	I	II	III	IV
Maternal dietary concentration (ppm)	0(carrier)	100	300	1000
Day 22 Postpartum				
Male rats	20	19a	20	20
Number of movements				
Block 1	67.4+12.0	75.5+10.8	68.8+9.3	68.0+10.0
Block 2	53.3+21.8	57.8+21.6	58.7+15.2	60.6+17.1
Block 3	47.8+28.0	46.6+26.9	50.6+23.1	56.2+17.5
Block 4	46.5+25.7	48.8+25.0	46.1+23.5	56.6+17.0
Block 5	48.2+28.8	48.5+21.4	43.4+24.0	54.2+22.0
Block 6	31.5+27.5	39.6+26.6	43.0+24.2	47.0+22.3
Block 7	31.6+24.7	36.0+29.1	35.6+26.4	51.9+22.0*
Block 8	40.8+31.5	35.0+28.2	37.4+26.9	53.2+25.1
Block 9	35.0+28.8	34.9+26.5	33.6+26.6	46.3+24.2
Block 10	25.6+24.2	31.7+22.4	27.6+27.1	42.8+22.8
Block 11	26.6+26.5	31.0+25.6	32.2+25.5	47.4+27.2*
Block 12	21.4+24.3	27.4+24.1	29.3+27.0	41.2+26.8*
Block 13	23.6+29.9	24.3+24.9	30.4+26.9	41.6+24.2
Block 14	23.0+24.2	20.0+26.2	24.1+25.3	37.8+25.0
Block 15	22.7+26.5	20.2+23.8	18.2+20.1	43.5+30.2*
Block 16	19.6+25.1	25.0+28.6	22.0+24.0	32.5+27.4
Block 17	22.8+28.2	21.7+23.7	22.9+23.5	36.6+30.3
Block 18	22.6+25.9	22.1+23.4	21.2+21.7	33.2+28.2
Total	610.2+357.3	646.2+222.0	645.0+258.2	850.5+280

Total = Sum of blocks; each Block consists of a 5 minute period.
a. Excludes values for rat 9317, which was not continued on study.
* Significantly different from the carrier group value ($p \leq 0.05$).

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TABLE F1 (page 10): Motor Activity - Summary - F1 Generation Rats - Subset 3

Maternal dosage Group	I	II	III	IV
Maternal dietary concentration (ppm)	0(carrier)	100	300	1000
Day 22 Postpartum				
Male rats	20	19a	20	20
Time (seconds) spent in movement				
Block 1	142.7±42.0	137.0±29.4	134.2±41.0	127.2±45.1
Block 2	94.8±54.0	85.7±40.9	98.8±49.2	98.3±42.6
Block 3	79.4±60.2	71.9±59.0	78.0±51.0	95.8±48.2
Block 4	76.0±52.1	67.4±51.4	78.6±56.5	94.8±45.7
Block 5	74.6±54.3	67.0±40.0	65.8±47.5	83.3±40.4
Block 6	42.4±51.6	56.7±55.2	60.6±47.5	81.8±57.6
Block 7	46.0±45.2	55.7±58.8	52.6±48.6	88.4±53.9*
Block 8	53.6±50.7	47.4±48.2	50.7±48.4	78.2±47.0
Block 9	63.9±72.2	51.8±55.6	42.8±41.8	65.8±43.0
Block 10	36.1±47.0	40.0±36.4	39.5±46.3	68.8±48.7
Block 11	46.4±61.3	35.7±33.6	46.7±42.6	66.8±46.9
Block 12	35.2±58.6	35.7±35.0	42.0±46.2	53.8±48.5
Block 13	36.0±54.2	33.7±40.0	42.6±43.1	54.8±39.5
Block 14	39.0±54.0	26.7±45.8	35.0±40.6	58.4±54.1
Block 15	34.4±53.7	24.7±35.2	27.0±36.4	58.1±50.0
Block 16	30.4±49.5	31.6±43.7	26.2±33.9	44.8±46.8
Block 17	30.3±42.5	28.7±41.3	29.7±43.8	49.8±46.3
Block 18	38.2±59.6	28.3±33.6	28.4±36.5	49.2±49.9
Total	999.6±791.9	925.8±429.5	979.6±524.4	1318.0±630.1

Total = Sum of blocks; each Block consists of a 5 minute period.

a. Excludes values for rat 9317, which was not continued on study.

* Significantly different from the carrier group value ($p \leq 0.05$).

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TABLE F1 (page 11): Motor Activity - Summary - F1 Generation Rats - Subset 3

Maternal dosage Group	I	II	III	IV
Maternal dietary concentration (ppm)	0(carrier)	100	300	1000
Day 22 Postpartum				
Female rats	20	19a	20	20
Number of movements				
Block 1	61.9±18.1	57.8±14.4	62.4±13.1	60.0±13.6
Block 2	53.6±20.7	59.3±12.3	55.1±18.1	59.9±11.8
Block 3	48.4±19.2	46.9±21.8	46.1±19.4	52.4±17.7
Block 4	42.6±22.3	42.4±26.7	45.1±21.4	52.4±14.0
Block 5	48.0±22.1	39.1±26.1	43.8±23.2	47.5±19.1
Block 6	43.7±23.1	40.4±21.6	42.2±21.9	46.9±17.2
Block 7	37.6±24.6	37.7±26.9	44.6±23.5	45.8±21.3
Block 8	34.8±24.6	35.9±27.8	35.4±21.4	42.0±22.8
Block 9	35.3±25.8	34.5±27.0	39.2±21.4	45.2±25.1
Block 10	28.4±26.0	29.2±26.7	28.6±22.9	40.6±30.1
Block 11	34.2±28.6	33.2±28.2	21.2±24.8	34.8±26.8
Block 12	23.2±22.4	29.4±29.4	28.2±29.0	32.1±23.8
Block 13	19.4±24.8	25.5±27.1	25.4±26.2	35.1±30.0
Block 14	23.4±29.7	19.0±23.5	22.4±27.7	29.2±30.6
Block 15	23.4±22.6	22.4±29.3	23.2±27.5	34.4±30.3
Block 16	20.3±22.4	18.2±20.7	21.4±27.7	31.9±28.1
Block 17	17.0±21.8	19.9±26.8	20.2±22.7	27.0±31.7
Block 18	23.4±27.1	17.3±23.0	13.4±19.8	21.4±25.5
Total	618.6±284.5	608.0±332.4	617.8±214.6	738.3±277.1

Total = Sum of blocks; each Block consists of a 5 minute period.
a. Excludes values for rat 9317, which was not continued on study.

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TABLE F1 (page 12): Motor Activity - Summary - F1 Generation Rats - Subset 3

Maternal dosage Group	I	II	III	IV
Maternal dietary concentration (ppm)	0(carrier)	100	300	1000
Day 22 Postpartum				
Female rats	20	19a	20	20
Time (seconds) spent in movement				
Block 1	127.2±42.1	122.5±44.6	118.4±36.2	116.8±43.3
Block 2	92.4±49.4	112.1±41.0	90.5±40.4	101.3±20.1
Block 3	70.6±32.9	75.8±45.4	63.0±39.8	81.2±37.3
Block 4	53.4±34.8	71.0±56.8	63.0±38.9	83.2±37.0
Block 5	69.3±45.6	66.5±58.3	55.0±34.6	62.6±38.2
Block 6	64.6±45.0	61.9±45.8	62.8±43.3	65.1±33.8
Block 7	55.5±45.2	58.3±46.6	58.0±35.0	66.8±44.3
Block 8	44.3±36.5	52.9±49.4	46.2±40.6	59.4±37.9
Block 9	44.6±39.9	44.1±40.8	55.5±36.0	68.7±44.8
Block 10	33.3±33.3	45.7±49.9	35.8±31.8	64.1±48.9
Block 11	46.8±42.3	39.1±42.4	27.5±35.7	56.5±51.3
Block 12	29.2±32.3	44.0±47.7	43.2±53.6	42.5±39.9
Block 13	25.2±39.1	37.7±47.2	33.3±44.1	60.0±57.7
Block 14	33.0±47.8	32.3±49.3	27.6±38.8	43.5±47.8
Block 15	33.4±40.0	35.1±51.9	31.6±42.6	53.6±56.0
Block 16	27.9±32.4	20.6±26.8	28.2±42.3	49.6±52.5
Block 17	22.6±33.7	28.7±44.8	25.6±34.6	35.0±45.5
Block 18	28.2±35.4	21.6±31.5	15.0±29.3	30.3±42.5
Total	901.4±434.0	970.2±643.6	880.1±365.1	1140.3±477.0

Total = Sum of blocks; each Block consists of a 5 minute period.
a. Excludes values for rat 9317, which was not continued on study.

Protocol 1702-004: Developmental neurotoxicity study of technical grade Tebuconazole administered orally via diet to Crl:CD(R)BR VAF/Plus(R) presumed pregnant rats (Sponsor's study number: 98-C612-QU)

TABLE F1 (page 13): Motor Activity - Summary - F1 Generation Rats - Subset 3

Maternal dosage Group	I	II	III	IV
Maternal dietary concentration (ppm)	0(carrier)	100	300	1000
Day 62 Postpartum				
Male Rats	20	19a	20	20
Number of movements				
Block 1	64.8±9.6	61.3±12.7	63.7±10.1	62.3±10.4
Block 2	67.1±10.2	65.8±8.1	65.5±9.0	66.8±9.0
Block 3	70.4±10.2	63.6±10.6	67.5±7.5	64.4±9.5
Block 4	67.0±9.8	67.3±10.5	67.8±10.6	69.6±10.1
Block 5	66.6±13.1	64.6±8.9	68.6±8.1	67.0±10.8
Block 6	68.1±11.0	60.8±17.4	67.6±12.2	66.8±12.9
Block 7	68.6±10.9	62.3±15.8	60.0±16.8	61.6±17.3
Block 8	66.0±14.7	58.6±21.8	59.6±20.9	63.2±17.2
Block 9	62.0±16.9	54.8±23.3	51.0±24.2	61.6±19.6
Block 10	60.8±17.3	55.5±27.8	49.9±21.9	55.0±25.6
Block 11	58.4±20.3	49.1±29.8	48.4±29.8	54.8±29.8
Block 12	52.9±23.1	48.4±29.4	34.4±31.7	48.1±26.0
Block 13	43.4±27.4	45.0±29.0	31.4±29.1	43.7±33.1
Block 14	37.4±30.0	35.0±31.8	28.6±31.4	44.1±33.3
Block 15	35.6±31.8	28.9±29.0	25.4±29.3	33.3±30.8
Block 16	35.7±33.7	20.7±26.2	23.0±26.2	30.4±31.6
Block 17	32.6±32.3	18.6±25.4	25.6±32.2	32.1±29.4
Block 18	25.4±33.1	16.6±23.1	21.2±27.1	27.7±32.2
Total	982.8±207.0	877.0±216.5	859.1±209.4	952.2±273.9

Total = Sum of blocks; each Block consists of a 5 minute period.
a. Excludes values for rat 9317, which was not continued on study.

Protocol 1702-004: Developmental neurotoxicity study of technical grade Tebuconazole administered orally via diet to Crl:CD(R)BR VAF/Plus(R) presumed pregnant rats (Sponsor's study number: 98-C612-QU)

TABLE F1 (page 14): Motor Activity - Summary - F1 Generation Rats - Subset 3

Maternal dosage Group	I	II	III	IV
Maternal dietary concentration (ppm)	0(carrier)	100	300	1000
Day 62 Postpartum				
Male Rats	20	19a	20	20
Time (seconds) spent in movement				
Block 1	216.4±26.0	210.6±35.0	216.0±24.4	217.4±26.1
Block 2	179.3±37.6	195.6±33.5	188.2±26.2	192.2±30.0
Block 3	164.7±42.4	181.7±47.7	183.4±33.4	171.4±39.3
Block 4	155.5±38.0	161.0±40.7	158.3±31.1	159.2±44.0
Block 5	155.6±41.9	150.4±51.9	154.2±37.1	154.2±43.3
Block 6	131.1±34.7	134.6±55.9	144.4±42.2	141.6±43.2
Block 7	126.7±33.9	123.5±55.0	113.8±51.4	133.4±47.7
Block 8	124.3±38.4	98.6±52.0	109.3±53.7	126.2±54.6
Block 9	109.4±44.9	93.0±55.1	79.0±59.3	118.6±58.2
Block 10	118.0±50.4	90.9±53.2	79.8±53.3	101.8±64.2
Block 11	99.9±57.6	97.3±72.2	85.8±67.5	88.8±58.1
Block 12	94.0±63.0	80.2±63.4	53.6±63.0	76.0±49.4
Block 13	70.7±60.0	74.6±58.4	42.6±48.7	59.8±58.0
Block 14	66.1±66.3	61.3±68.5	50.2±68.4	72.6±70.2
Block 15	50.6±53.8	50.5±66.9	34.4±49.4	54.2±64.0
Block 16	49.6±57.1	31.8±50.2	31.4±47.8	56.6±75.8
Block 17	52.7±67.6	28.3±52.6	44.3±66.0	47.8±59.0
Block 18	41.7±64.8	24.9±44.0	37.6±57.9	44.4±65.7
Total	2006.2±465.9	1888.9±684.0	1806.4±588.9	2016.2±594.6

Total = Sum of blocks; each Block consists of a 5 minute period.
a. Excludes values for rat 9317, which was not continued on study.

Protocol 1702-004: Developmental neurotoxicity study of technical grade Tebuconazole administered orally via diet to Crl:CD(R)BR VAF/Plus(R) presumed pregnant rats (Sponsor's study number: 98-C612-QU)

TABLE F1 (page 15): Motor Activity - Summary - F1 Generation Rats - Subset 3

Maternal dosage Group	I	II	III	IV
Maternal dietary concentration (ppm)	0(carrier)	100	300	1000
Day 62 Postpartum				
Female Rats	20	19a	19b	20
Number of movements				
Block 1	62.8±6.3	62.7±10.2	59.6±9.1	60.6±7.6
Block 2	67.0±9.1	65.7±11.7	64.2±7.8	64.4±11.2
Block 3	65.4±10.0	67.3±11.7	63.4±8.2	64.2±7.3
Block 4	66.6±8.1	65.6±10.2	65.4±8.9	61.6±8.0
Block 5	67.4±7.4	68.7±8.6	66.7±8.8	66.8±8.0
Block 6	63.6±9.3	65.5±15.9	62.5±11.4	65.3±9.9
Block 7	66.7±12.9	61.7±17.9	62.5±16.6	63.6±8.5
Block 8	62.6±15.2	60.1±22.0	55.3±24.4	64.2±9.3
Block 9	56.8±22.7	59.5±24.8	58.5±22.4	58.9±19.8
Block 10	46.8±25.7	54.5±23.7	51.4±23.6	58.0±17.1
Block 11	43.2±29.0	50.1±28.1	47.2±27.5	58.4±20.8
Block 12	43.9±28.6	45.8±30.8	40.7±26.3	43.4±26.5
Block 13	36.6±30.0	41.7±32.7	37.7±35.1	36.8±30.9
Block 14	36.4±30.2	40.8±32.4	39.1±34.8	34.8±32.2
Block 15	35.4±30.6	25.8±32.2	26.5±30.4	38.6±33.0
Block 16	35.8±26.2	25.0±29.3	30.3±28.5	36.1±33.3
Block 17	28.8±27.9	25.7±30.7	33.8±31.1	27.9±29.9
Block 18	24.0±23.6	24.0±31.5	34.7±26.8	23.2±23.6
Total	909.9±185.2	910.5±240.3	899.4±191.6	926.9±211.2

Total = Sum of blocks; each Block consists of a 5 minute period.
a. Excludes values for rat 9317, which was not continued on study.
b. Excludes values for rat 9780, which was missing on day 23 of study; was found and sacrificed on day 33 or study.

Protocol 1702-004: Developmental neurotoxicity study of technical grade Tebuconazole administered orally via diet to Crl:CD(R)BR VAF/Plus(R) presumed pregnant rats (Sponsor's study number: 98-C612-QU)

TABLE F1 (page 16): Motor Activity - Summary - F1 Generation Rats - Subset 3

Maternal dosage Group	I	II	III	IV
Maternal dietary concentration (ppm)	0(carrier)	100	300	1000
Day 62 Postpartum				
Female Rats	20	19a	19b	20
Time (seconds) spent in movement				
Block 1	217.2±20.5	216.0±24.0	227.3±26.6	228.4±18.8
Block 2	196.8±21.8	186.5±37.3	195.9±30.5	196.8±32.2
Block 3	175.4±34.8	196.2±38.9	187.5±35.7	188.0±29.3
Block 4	153.4±32.6	168.7±34.1	162.4±26.0	166.3±35.3
Block 5	147.5±27.4	158.6±39.8	159.5±35.9	158.5±37.9
Block 6	134.0±43.1	143.7±52.4	140.0±52.0	148.8±39.5
Block 7	122.0±31.0	118.0±53.0	117.6±47.7	146.5±41.9
Block 8	125.1±46.6	121.7±64.1	117.3±67.3	152.6±39.5
Block 9	93.3±49.2	104.5±59.3	126.0±57.7	121.0±53.4
Block 10	64.0±45.6	98.9±65.4	93.2±65.7	109.6±46.2*
Block 11	77.4±61.6	100.9±70.6	97.7±75.3	97.0±48.8
Block 12	67.7±54.8	85.6±67.1	82.6±76.0	70.8±56.1
Block 13	59.7±61.9	60.3±55.0	64.7±66.4	51.6±48.8
Block 14	59.2±61.4	61.0±58.2	63.2±66.1	57.7±62.2
Block 15	54.0±56.2	39.7±58.0	42.1±55.0	63.7±64.4
Block 16	50.0±49.6	38.7±56.8	54.7±60.8	55.0±56.1
Block 17	45.4±61.2	41.9±60.7	63.7±68.8	55.3±67.1
Block 18	33.0±46.9	36.2±54.3	51.4±54.8	32.0±40.5
Total	1875.0±401.8	1977.0±617.2	2046.9±616.5	2099.8±463.7

Total = Sum of blocks; each Block consists of a 5 minute period.
a. Excludes values for rat 9317, which was not continued on study.
b. Excludes values for rat 9780, which was missing on day 23 of study; was found and sacrificed on day 33 or study.

APPENDIX B

Submitted Positive Control Data

A volume of information was submitted as positive control data for the current study. Most of the information in this volume consisted of summaries of studies performed by scientists currently or formerly affiliated with the study laboratory. Some of the studies were performed at the study laboratory, others at institutions with which the scientists were previously affiliated.

The summarized information included a variety of studies (summarized briefly below), largely relevant to the development of the procedures used in the current developmental neurotoxicity and adult neurotoxicity study protocols at the study laboratory. However, apart from specific exceptions described below, the submitted information is not fully adequate to support the sensitivity of many of the procedures used in the current study.

Our current recommendations for positive control data are as follows:

> Appropriate, adequate positive control data from the laboratories that performed the Developmental Neurotoxicity studies should be provided to the Agency at the time of study submission. These positive control data should demonstrate the sensitivity of the procedures used, including the ability to detect both increases and decreases in parameters measured, as appropriate. While the positive control studies do not need to be performed using prenatal exposures, the laboratory must demonstrate competence in the evaluation of effects in neonatal animals perinatally exposed to chemicals and establish test norms for all critical endpoints, and for appropriate age groups. The positive control data should be derived from relatively recent studies, that is, studies that were performed in the same laboratory within the past few years, utilizing (to the greatest extent possible) the staff and equipment that will be used in conducting the current studies.

Based on our review of the submitted information, most of the submitted studies were performed outside of the recommendated time frame, and laboratory personnel varied from those involved in the current study. It is unclear whether test procedures were the same as those used in the current study, and not all procedures were evaluated following exposure to neurotoxic substances. Insufficient information was included for most studies; for example, individual animal data were rarely included and detailed procedural information was often not provided.

Since treatment-related effects were seen at all doses evaluated in the current study, we will not require submission of additional positive control data prior to acceptance of that study. We note, however, that insufficiently sensitive procedures could lead to a failure to detect effects on some parameters (for example, cognitive or motor activity testing) or a failure to detect effects at low doses.

Based on our evaluation of the submitted positive control data, according to current recommendations, additional data are needed to adequately validate the sensitivity and reliability of the procedures listed below, as currently used in the testing laboratory. The additional positive control data should be gathered using current personnel and equipment, with the same

procedures as those used in the study, and using the same strain of rat. Complete study reports should be submitted, including individual animal data.
Procedures lacking appropriate positive control data:

1) Motor activity evaluation, all time points;
2) Learning and memory procedures, both time points;
3) Auditory startle habituation, both time points;
4) Neuropathology evaluations:
    -qualitative evaluations in treated pups
    -morphometric evaluations in adults (late time point).

As noted below, the submitted positive control data for pup morphometric evaluations was considered adequate (Study #12), but the submission for adult qualitative evaluations was incomplete, since the data tables were not provided. The adequacy of the data supporting adult qualitative evaluations cannot be determined in the absence of the data tables; those data should be submitted.

Summary of submitted studies

Each of the submitted studies, along with a brief description, is listed below. Studies are grouped according to the type of data included.

FOB validation studies

1. Parker, R.M. (1999) Neurotoxicity evaluation of positive control substances in Crl:CD®BR VAF/Plus Rats. Argus Research Laboratories, August 6, 1999, Unpublished study.

[Appendix O, Section 10, pp. 954-1131]

The study evaluated FOB performance using several known neurotoxic chemicals (acrylamide, Trimethyl tin, MK-801, Carbaryl, and DDT). Evaluations were made in 59-day old rats. This appears to be a GLP study, useful in validating FOB evaluations in adult rats. However, it was not possible to fully evaluate the adequacy of these data, because the portion of the report containing the individual animal data was excluded from the submission (study report pp. 143-229). Since full FOB evaluations were not performed in the current study, these data are not considered critical in support of this study.

2. Protocol 012-015: Neurotoxicity evaluation of DDT in Crl:CD®BR VAF/Plus Rats.

[Appendix O, Section 11, pp. 1133-1141]

This study was performed in 1992 at Argus Laboratories, and evaluated 50/51 day old rats on the FOB. As above, these data are relevant to FOB evaluations performed in adult rats, which were not performed in the current study.

FOB and motor activity in adult rats

3. Lochry, E.A., J.A. Foss, and M.S. Christian (1990). Validation of a functional observational battery and motor activity measure using positive test substances. Argus Research Laboratories, Poster presented at the Annual Meeting of the American College of Toxicology, Orlando, Florida, October 1990.

[Appendix O, Section 12, pp. 1142-1174]

This information consists of a poster copy. The study described was performed on rats which were 65 days old at arrival in the laboratory (age at testing was not stated), and concerns performance of FOB and motor activity measures following administration of DDT, physostigmine, and acrylamide.

4. Protocol 012-014: Neurotoxicity evaluation of positive control substances in Crl:CD®BR VAF/Plus Rats.

[Appendix O, Section 13, pp. 1176-1242]

This submission consisted of summary data only, concerning FOB and motor activity testing using acrylamide and carbaryl.

Studies including assessments in developing animals

5. Foss, J.A. and E.A. Lochry. (1991) The assessment of motor activity in neonatal and adult rodents using passive infrared sensors. Argus Laboratories, Poster present at the Annual Meeting of the American College of Toxicology, Savannah, Georgia, October, 1991.

[Appendix O, Section 14, pp. 1243-1250]

This section consists of a poster copy. Habituation (for motor activity) was evaluated in adult rats and mice, and in neonatal rats. Several test substances were evaluated for adult rats (including acrylamide, IDPN, DDT, and triadiamefon), but neonates were untreated, and evaluated on several different days (13, 17, 21, and 58/59). Test sessions were 60 minutes long, with 5 minute subsessions. Summary data only were presented, and it was not clear whether significant differences were detected between days for the neonates (the poster stated only that differences were detected across time within a session).

6. Untitled.

[Appendix O, Section 15, pp. 1251-1289]

The submitted study evaluated motor activity, auditory startle, and neuropathology following treatment with acrylamide, amphetamine, TMT, and MK-801; only the motor activity data for acrylamide and amphetamine were submitted. The date of the study and personnel involved were not listed. Age of tested animals was not stated, although the weights (approximately 430 g for males and 250 g for females, pre-dosing) would indicate that adult rats were used. Motor activity data were presented as means, following treatment with acrylamide [45 mg/kg, for a maximum of 10 days], or amphetamine [0.75 mg/kg]. Testing was conducted in stainless-steel

wire-bottomed cages, using passive infrared sensors; testing sessions were 90-minutes in duration, with data tabulated for each 5 minute interval. Activity levels were decreased following acrylamide treatment, and increased following amphetamine treatment.

7. Lochry, E.A. and E.P. Riley. (1980) Retention of passive avoidance and T-maze escape in rats exposed to alcohol prenatally. Neurobehavioral Toxicology 2:107-115.

[Appendix O, Section 16, pp. 1291-1299]

This was a published study, performed at the State University of New York at Albany, evaluating performance in passive avoidance and T-maze following prenatal exposure to alcohol.

8. Lochry, E.A., J.A. Foss, and M.S. Christian. (1990). Learning and retention paradigms in developmental neurotoxicity test batteries: passive avoidance and watermaze. Argus Research Laboratories, Poster presented at the 18th European Teratology Society Conference, Edinburgh, Scotland, September 1990.

[Appendix O, Section 17, pp. 1300-1305]

The submitted information consists of a copy of a poster, presenting information on the performance of weanling rats in passive avoidance and adult rats in a watermaze. The submission includes several tables of control data (performance of untreated rats), with statistical information regarding the variance of results. Minimal procedural information was provided.

9. Foss, J.A., E.A. Lochry, and A.M. Hoberman. (1990) Automated monitoring systems for motor activity and auditory startle applicable for both developmental and adult neurotoxicity studies. Argus Research Laboratories, poster presented at the 8th Inernational Neurotoxicology Conference, Little Rock, AK, October 1990.

[Appendix O, Section 18, pp. 1307-1320]

The submitted information consists of a copy of a poster (summary data only). Motor activity was evaluated on days 13, 17, 21, and 60 using 90 minute sessions; only untreated animals were evaluated. Apparently statistical evaluation was used to confirm habituation within sessions, no evaluation was made for differences across days. Similarly, auditory startle habituation was evaluated in untreated animals, on days 22 and 60. Habituation was demonstrated on day 60 for females, on both days for males. Minimal procedural information was included.

10. Foss, J.A. and E.P. Riley. (1989) Elicitation and modification of the acoustic startle reflex in animals prenatally exposed to cocaine. Neurotoxicology and Teratology 13:541-546.

[Appendix O, Section 19, pp. 1321-1327]

The submitted information consists of a published article, reporting a study performed San Diego State University. The potential for changes in the acoustic startle reflex was evaluated in adult

rats following prenatal exposure to cocaine; no effects from exposure to test substance were demonstrated.

11. Lochry, E.A., Hoberman, A.M., and Christian, M.S. (1985). Detection of prenatal effects on learning as a function of differential criteria. Neurobehavioral Toxicology and Teratology 7:697-701.

[Appendix O, Section 20, pp. 1328-1333]

The submitted information consists of a published article, from 1985, with different authors from the current study, although it was performed at Argus Research Laboratories. In the study, 20-day old pups were tested in a water maze that appears similar to that used in the current study. Several different learning criteria were evaluated, and it was determined that sensitivity of the test procedure for detecting changes in behavior following treatment with test substance depended on the specific learning criteria used (i.e. how many consecutive correct trials were required).

The age at testing was different from that used in the current study, and the procedure appears to have been slightly different. In particular, the authors were not able to demonstrate sensitivity of the test to prenatal alcohol exposure using a learning criteria of 5 consecutive correct trials (the criteria used in the current study). This study is not sufficient to document sensitivity of the procedure as performed in for the current study, and does raise concern about the sensitivity of the current procedures to detect test-material related effects.

Neuropathology, day 12 and adult

12. Neuropathology validation

[Appendix O, Section 21, pp. 1334-1391]

This section was provided by Dr. Robert Garman, of Consultants in Veterinary Pathology, who performed the neuropathological evaluations in the submitted study. The submission consisted of biographical and professional information regarding Dr. Garman, a validation study of adult neuropathological procedures following treatment with acrylamide, TMT, and MK-801, and a validation study comparing morphometric evaluations on untreated day 12 and day 10 neonatal rats. In addition, a copy of a poster was submitted (p. 1392, authors listed as Foss, Hoberman, and Christian, with neuropathological evaluations performed by Dr. Garman, dated 1992), evaluating neuropathology in adult rats following prenatal exposure to lead nitrate.

The validation study for adult neuropathology was missing the data tables, which show the number and type of lesions detected in evaluated rats (these data were listed in the report table of contents as starting on p. 34, but the submitted report ended on p. 33). Since these data are critical in documenting the sensitivity of the study procedures, the results of the study could not be fully evaluated. No validation was included for qualitative neuropathological evaluation of neonatal (day 12) rats, and no neuropathological alterations (or functional effects) were detected in adult rats following prenatal exposure to lead nitrate. The validation comparing day 10 and day 12 neonatal rats for morphometric measurements was performed on control rats only, and did not demonstrate ability to detect changes following neurotoxic insult. It did, however,

demonstrate the ability of the laboratory to detect changes in morphometric measurements from day 10 to day 12.

This submission provides useful information regarding the sensitivity of the morphometric procedures in pups. In addition, submission of the missing data tables should provide data regarding the sensitivity of the qualitative neuropathological evaluation for adult animals.